EDITORIAL

265 Ethambutol Optic Neuropathy: How We Can Prevent 100,000 New Cases of Blindness Each Year
Alfredo A. Saclun and Michelle Y. Wang

ORIGINAL CONTRIBUTIONS

269 Incidence and Clinical Features of Ethambutol-Induced Optic Neuropathy in Korea
Eun Ji Lee, Seong-Joon Kim, Ho Kyung Choang, Jeong Hun Kim, and Young Suk Yu

278 Multifocal Electroretinographic Abnormalities in Ethambutol-Induced Visual Loss
Yao Liu, Marc J. Dinkin, John I. Loewenstein, Joseph F. Rizzo, and Dean M. Cesari

283 Skew Deviation as the Initial Manifestation of Left Paramedian Thalamic Infarction
Edward Margolin, Dana Hamfan, Mary K. Berger, Omar R. Ahmad, Jonathan D. Trobe, and Stephen S. Gebarski

287 Periodic Alternating Nystagmus and Periodic Alternating Skew Deviation in Spinocerebellar Ataxia Type 6
Chaim B. Colen, Anastasia Ketko, Edwin George, and Gregory P. Van Slavern

289 Spontaneous Intracranial Hypotension Presenting as a Reversible Dorsal Midbrain Syndrome
Marco Fedi, Roberto Castello, Neil H. Shuey, L. Anne Mitchell, Cristoforo Comi, Francesco Monaco, and Mavizio Versino

293 Ocular Dipping in Creutzfeldt-Jakob Disease
Seong-Hae Jeong, SangYun Kim, Seong-Ho Park, and Ji Soo Kim

296 Binocular Vertical Rectus Muscle Recession For Comitant Vertical Strabismus
Oliver Bergami, Maria Gabriela Wirth, and Klara Landau

302 Ocular Misalignment in Graves Disease May Mimic That of Superior Oblique Palsy
Vicki M. Chen and Linda R. Dasig

305 Impairment of Vertical Saccades From an Acute Pontine Lesion in Multiple Sclerosis
Alessandra Rufa, Alfonso Cerase, Lorenzo Di Santi, Marco Mandala, Daniele Nuti, Antonio Giorgio, and Pasquale Annunziata

308 Perimetry While Moving the Eyes: Implications for the Variability of Visual Field Defects
Armin Toepfer, Erich Kasten, Tobias Guentheri, and Bernhard A. Sabel

(continued on next page)
Contents (continued)

320 Anatomic Characteristics of the Ophthalmic and Posterior Ciliary Arteries
Senem Evdogmus and Figeu Govsa

PHOTO ESSAYS

325 Suprasellar Hemangioblastoma
Shim Miyata, Takeshi Mikimi, Yoshihim Minamida, Yukinori Akiycmia, and Kiyohiro Houkin

327 Dilated Superior Ophthalmic Veins and Posterior Ischemic Optic Neuropathy After Prolonged Spine Surgery
Ashvini Redely, Rod Foroozan, Jane C. Edmond, and Lisa K. Hinckley

HYPOTHESIS

329 Saccadic Burst Cell Membrane Dysfunction Is Responsible for Saccadic Oscillations
AasefG. Shaikh, Stefano Ramat, Lance M. Opt icon, Kenichiro Miura, R. John Leigh, and David S. Zee

THE FIRST JACOBSON LECTURE

337 Familial Idiopathic Intracranial Hypertension
James J. Corhetl

NEURO-OPHTHALMOLOGY AT LARGE

348 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO), Fort Lauderdale, April 27-May 1, 2008
Howard D. Poiicrcinz, Raghn Mudiimbai, and Kenneth S. Shindler

Wen-Ying Wu-Chen and Mark L. Master

May-Yung Yen

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LETTER TO THE EDITOR
359 Delayed Third Cranial Nerve Palsy After Aneurysm Wrapping
Zinti Evy Aimer and Neil R. Miller
359 Anticholinergic Esotropia
Jennifer M. Anderson and Michael C. Brodsky

BOOK REVIEWS
Karl Golnik
361 Eye Movement Disorders
Janet Rucker
Steven A. Newman
363 Handbook of Pediatric Neuro-Ophthalmology
Grant T. Liu
363 Neuro-Ophthalmology. Neuronal Control of Eye Movements
Agnes Wong
Michael X. Replca
364 Strabismus Surgery and Its Complications
Sean P. Donahue
365 Neurology Board Review. An Illustrated Study Guide
Jonathan D. Trobe
365 Fundamental Neuroscience for Basic and Clinical Applications, 3rd Edition
Kevin A. Kerber
366 The Clinical Neuropsychiatry of Multiple Sclerosis, 2nd Edition
Myla D. Goldman
366 Minimally Invasive Neurosurgery
Edward R. Laws
367 The Massachusetts General Hospital Handbook of Neurology, 2nd Edition
Madaline Harrison
368 Intracranial Arteriovenous Malformations
Nina J. Solenski and Aaron S. Dumont
369 The Dementias 2
Carol A. Manning
369 On Being a Doctor 3
August L. Reader III
371 CALENDAR
373 ACKNOWLEDGMENT OF REVIEWERS
Endovascular Treatment of Dural Carotid Cavernous Sinus Fistulas

Ajay K. Wakhloo, MD, PhD

With the introduction of newer embolization materials and flat panel detectors to the surgical angiography unit and refinement of endovascular techniques, we are witnessing rapid improvement in the safety and efficacy of treatment of direct and dural carotid-cavernous sinus fistulas (CCFs). In this issue of the Journal of Neuro-Ophthalmology, Gemmete et al (1) provide an overview on the clinical presentations, Barrow classification, and typical CT and MRI findings of CCFs. The authors then focus on the history of endovascular CCF treatment and introduce us to transarterial, transvenous, and combined transarterial-transvenous approaches. They point out that treatment options range from manual compression of the carotid artery, radiation therapy, stent and stent grafts (predominantly for direct CCFs), placement of detachable balloons or coils within the arteriovenous connection, and infusion of embolic materials into the CCF. Depending on the experience and preference of the treating physician, embolic materials are frequently combined.

The articles by Gandhi et al (2) and Bhatia et al (3) describe the use of Onyx for dural CCF. Recently approved by the Food and Drug Administration (FDA) for preoperative embolization of brain arteriovenous malformations (bAVMs), Onyx is an ethylene vinyl alcohol copolymer in a dimethyl sulfoxide solvent. This liquid embolic mixture also contains suspended tantalum powder that gives it radioopacity and its trademark black color. Onyx is a nonadhesive polymer that precipitates in the vessel as the solvent is diluted and washed out. The authors emphasize the safety profile of Onyx resulting from the nonadhesive nature of the material, which permits a long and controlled infusion and a significant reduction in procedure time and radiation exposure.

Although a controlled and long injection is desirable, it entails the risk of occluding pial arteries through dural anastomoses. Unlike cyanoacrylates, which are mixed with iodinated oil and well visible (4), Onyx may be poorly visualized in smaller vessels owing to sedimentation of tantalum powder within the delivery microcatheter. This feature demands advanced knowledge of “dangerous” preexisting extracranial-intracranial anastomoses frequently not visible before embolization. Gandhi et al (2) and Bhatia et al (3) emphasize the danger of Onyx infusion into preexisting collateral vessels. To avoid reflux of the embolic agent, use of a nondetachable temporary balloon within the internal carotid artery is recommended if the pretreatment angiogram shows that the fistula is substantially supplied by the meningohipphyseal trunk.

Although 6 patients treated successfully is a small number, the authors provide evidence that Onyx is a promising new embolic agent for treatment of dural CCFs. Several studies have now been published on the successful use of Onyx alone or in conjunction with coils and stents for direct and dural CCFs and other dural arteriovenous fistulas (AVFs) (5–10). Although cure of dural CCFs and other AVFs is reported in most treated patients with no major periprocedure morbidity, large series demonstrate that the treatment of AVMs remains challenging (5–11). Although use of Onyx was initially promising, larger case series show that cure of bAVMs with Onyx is achieved in only 2%–28% of patients, and...
there is permanent morbidity and mortality of 3% to 11%. In experienced hands, an increased cure rate may be attainable, but the complication rate remains comparable to that of formerly used liquid embolic agents (11,12).

As Bhatia et al (3) discuss, endovascular treatment of dural CCFs can be lengthy and may involve significant radiation exposure owing to the time needed to place the microcatheter in hard-to-access dural CCFs rather than to the time needed to deploy embolic materials. As the numbers of x-ray-based endovascular procedures increase, there is a growing concern about long fluoroscopy exposure (13,14). The goal remains to avoid skin injuries and damage to the lens from increased radiation exposure. In a recent study, the surface doses recorded during endovascular procedures were equivalent to a dose of 1.5 Gy, which may increase the risk of inducing meningiomas, gliomas, and nerve sheath tumors (15).

Experience over the past 3 decades has shown that endovascular treatment of CCFs is safe and should be considered the primary option. However, as with any new technology, caution is warranted with the latest embolic material until more patients have been treated. Long-term clinical and angiographic data on Onyx are needed to verify the permanency of CCF occlusion. As with cyanoacrylates, Onyx seems to generate a chronic inflammatory response, which may be important for lasting obliteration of any type of arteriovenous fistula (16,17).

REFERENCES

Successful Treatment of Six Cases of Indirect Carotid-Cavernous Fistula with Ethylene Vinyl Alcohol Copolymer (Onyx) Transvenous Embolization

Kartik D. Bhatia, MBBS, Lily Wang, MBBS, Richard J. Parkinson, MBBS, FRACS, and Jason D. Wenderoth, BSc, MBBS, FRANZCR

Background: Endovascular transvenous treatments have become the mainstay in the management of indirect carotid-cavernous fistulas (CCFs). However, the standard coil techniques are associated with a substantial failure and complication rate. The ethylene vinyl alcohol copolymer (Onyx) Liquid Embolization System has advantages over coils, including the ability to penetrate and occlude vessels of small caliber or with difficult access.

Methods: This was a review of 5 consecutive patients with indirect type D CCFs who underwent 6 procedures using the Onyx system alone at the Prince of Wales Hospital, Sydney, between December 2005 and May 2007. The cavernous sinus was catheterized with MTI Echelon-10 or Rebar-14 microcatheters via the femoral vein using an inferior petrosal approach to the cavernous sinus in 5 procedures and directly via the superior ophthalmic vein in 1 procedure.

Results: All 5 patients had complete closure of the fistulas as seen on imaging and full reversal of ophthalmic manifestations without lingering complications and with substantially shorter procedure times than with conventional approaches.

Conclusions: The Onyx system is a safe and useful method of closing indirect CCFs transvenously. This is the first series report of the use of the Onyx system alone in the treatment of these vascular abnormalities.


Carotid-cavernous fistulas (CCFs) are uncommon but clinically significant vascular anomalies that may be associated with serious neurologic or ophthalmic morbidity. The most commonly used classification system of CCFs is that proposed in 1985 by Barrow et al (1), consisting of four different grades (A–D) based on angiographic identification of the arterial feeding sources of the fistula (1,2). All 6 cases of the indirect CCFs in this series were Barrow type D fistulas, defined as having arterial feeding sources from both the internal carotid artery (ICA) and external carotid artery (ECA) (1–3).

Endovascular treatments have become the mainstay in the management of indirect CCFs over the last 20 years (2–7). The occlusion of the complex vessel network via endovascular approaches using standard balloon and coil techniques has been difficult, however, because the honeycomb morphology of the cavernous sinus is not amenable to these large and stiff devices, and the result sometimes is incomplete closure of the fistula with resultant worsening in morbidity associated with shunting into orbital or cortical venous systems (2,4,6,8–10). In addition, coil and balloon techniques are associated with a high rate of mechanical cranial nerve injury (4,5).

Liquid embolic systems such as pure ethanol and n-butyl cyanoacrylate (nBCA) are increasingly being used as adjuncts or alternatives to balloon and coil systems owing to the liquid’s ability to penetrate and occlude vessels of small caliber or with difficult access (11–13). However, the liquid poses a small but significant risk of venous and arterial thromboembolism via spontaneous droplet movement (11,13).

The ethylene vinyl alcohol copolymer (EVOH, Onyx) liquid embolization system (MicroTherapeutics Incorporated, Irvine, CA) uses a polymer that precipitates into an artificial embolus upon contact with blood or bodily fluids (12,14,15). This system possesses all of the advantages of other liquid embolic systems but allows greater control of polymer distribution, thus potentially reducing the risk of spontaneous droplet movement. It can fill cavities in a manner similar to that of foam-based embolization products (12,14,15). Unlike nBCA, Onyx also precipitates in a coherent fashion rather than having a tendency to
fragment. It can be delivered over much more prolonged periods because of its nonadhesive nature (14,15,16). The relative simplicity of CCF occlusion with Onyx compared with standard coil occlusion techniques has the potential to reduce angiographic screening times and thereby patient radiation dose.

We present 6 type D CCFs in 5 patients treated only with the Onyx system via a transvenous approach.

METHODS

Five consecutive patients with indirect type D CCFs were treated from December 2005 until May 2007 at the Prince of Wales Hospital, Sydney, Australia, using the Onyx system via a transvenous approach. Three of the patients were women, aged 44, 54, and 64 years at the time of treatment, and two were men, aged 63 and 64 years at the time of treatment. All endovascular procedures were undertaken by experienced neurovascular interventionalists (JW and RP).

Onyx was chosen as the sole embolization agent for these patients because of its theoretical advantages in reducing screening times, its ease and flexibility of use, and the theoretical reduction in risk of incomplete closure, cranial nerve injury, adhesive complications, and thromboembolism. In none of the 6 patients was there a need to use alternative embolic products.

The Onyx system consists of a copolymer that is dissolved in a dimethyl sulfoxide (DMSO) solvent (15). Within this mixture there is a suspended micronized tantalum powder that allows fluoroscopic visualization. When this liquid mixture is delivered via a catheter to the desired site, it makes contact with blood that causes the DMSO solvent to diffuse away rapidly, resulting in precipitation of the EVOH polymer into a putty-like mass with radiopaque properties (12,15). The nature of the precipitation process is such that the layer of Onyx in contact with blood forms a skin, the center of the precipitating mass remaining in its dissolved state (15). As pressure is applied to the delivery syringe, the liquid Onyx ruptures the overlying skin at its weakest points much as lava flows occur on the ocean floor. The specific formulation used in this series was Onyx-34, which has a nominal liquid viscosity of 34 centistokes (15). This formulation has relatively high viscosity so as to reduce the risk of retrograde penetration into the ICA.

In our patients, the liquid was delivered by an MTI Rebar-10 microcatheter in Case 1 and by an MTI Echelon-10 microcatheter in all other cases in accordance with the manufacturer’s instructions (15).

All 5 patients had pretreatment imaging of the fistulas via time-resolved magnetic resonance angiography (TR-MRA) and digital subtraction angiography (DSA). All catheterization was completed under full anticoagulation using heparin to achieve an activated clotting time of 250–300 seconds. All procedures were performed under general anesthesia. DSA was used to obtain views of right and left internal carotid, external carotid, and vertebral arteries before treatment via catheterization of the femoral artery.

A catheter was maintained in the arterial system at all times to allow visualization of the arterial side of the fistula. The diagnostic angiograms were closely studied for supply of the fistulas by inferolateral or meningohypophyseal branches of the ICA. Such supply would be a relative contraindication to the use of Onyx or would necessitate the use of balloon protection in the ICA during Onyx injection.

The cavernous sinus was catheterized via the femoral vein using an inferior petrosal approach in 5 procedures. In 1 patient, in whom there were bilateral CCFs, a second treatment was required, necessitating access to the opposite cavernous sinus via the superior ophthalmic vein, which was cannulated under transorbital ultrasound guidance.

The initial targeted point of embolization in all cases was the venous point that filled first on contrast injection from the arterial side of the fistula, but this was not always necessary. Onyx-34 was progressively delivered into the cavernous sinus until complete obliteration of the sinus and the fistula was achieved.

The average angiographic screening time for the 5 procedures was 36.58 minutes. In 1 procedure, the screening time could not be obtained because of equipment failure. Confirmatory post-Onyx DSA films were obtained from the arterial supply to demonstrate definitive closure of the fistula. All patients were examined after the procedure to assess the efficacy of the treatment by imaging and clinical criteria. Follow-up included MRI and ophthalmologic evaluation at 3 months after treatment.

RESULTS

Table 1 shows clinical and imaging features of our 5 patients.

Case 1

A 63-year-old man had a 2-week history of redness of the right eye. Four days before presentation, he had noted double vision on looking to the right and then began to have a progressive reduction in the vision of his right eye. He was found to have ptosis, exophthalmos, and chemosis of the right eye. There was a significant reduction in visual acuity in the right eye. Diplopia was present on right, upward, and downward gaze, and there was an obvious abduction deficit of the right eye. There were no other pertinent clinical abnormalities.

TR-MRA showed a right-sided Barrow type D CCF fed by right ICA and ECA branches (Fig. 1A–B). Given the rapid progression in symptoms and the risk of blindness to
TABLE 1. Clinical and imaging features of our 5 patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Clinical Presentation</th>
<th>Fistula Side</th>
<th>Venous Approach</th>
<th>Procedure Time (min)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>M</td>
<td>Diplopia, right eye visual loss</td>
<td>Right</td>
<td>IPS</td>
<td>37.6</td>
<td>Temporary sixth cranial nerve palsy</td>
</tr>
<tr>
<td>2</td>
<td>54</td>
<td>F</td>
<td>Diplopia, pulsatile tinnitus, left eye visual loss</td>
<td>Left</td>
<td>IPS</td>
<td>N/A</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>F</td>
<td>Headache, pulsatile tinnitus, diplopia, left eye visual loss</td>
<td>Right</td>
<td>SOV</td>
<td>23.7</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>F</td>
<td>Diplopia</td>
<td>Right</td>
<td>IPS</td>
<td>39.1</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>M</td>
<td>Diplopia, right eye conjunctival corkscrew vessels</td>
<td>Right</td>
<td>IPS</td>
<td>22.5</td>
<td>None</td>
</tr>
</tbody>
</table>

IPS, inferior petrosal sinus; SOV, superior ophthalmic vein; N/A, not available.

the right eye, he underwent endovascular management of the lesion with the Onyx system the next day.

Transvenous embolization was achieved using the Onyx-34 Liquid Embolization System with an MTI Rebar-10 catheter via an inferior petrosal approach from the right femoral vein. The cavernous sinus was progressively and completely obliterated with Onyx. Post-Onyx DSA views demonstrated definitive closure of the fistula (Fig. 1C). Total screening time was 37.6 minutes. There was an immediate dramatic reversal in the proptosis and chemosis of the right eye. Postoperatively the patient was noted to have a right sixth cranial nerve palsy, unchanged when compared with his preprocedural status. However, on follow-up examination at 3 months, the palsy had completely resolved. Successful closure of the fistula was confirmed on follow-up MRI examination.

Case 2
A 54-year-old woman presented with a 3-week history of blurred vision and painful movements of the left eye. For 10 days before presentation, she had had double vision upon looking to the left and a persistent whooshing sound in both ears. She was found on examination to have reduced visual acuity, conjunctival congestion, and mild proptosis of the left eye. There was also reduced abduction of the left eye. Noncontrast CT imaging revealed dilated superior ophthalmic veins bilaterally.

DSA demonstrated a complex left type D CCF with arterial supply bilaterally from the ICA and ECA (Fig. 2A–B). There was also a right type D CCF. The left cavernous sinus was accessed via an inferior petrosal approach from the right femoral vein and was successfully embolized using the Onyx-34 Liquid Embolization System with an

FIG. 1. Digital subtraction angiography of Case 1. Midarterial (A) and late arterial (B) phase lateral right internal carotid arteriograms show fistulous opacification of the right cavernous sinus (arrow) and superior ophthalmic vein (arrowhead). Lateral right internal carotid arteriogram (C) after the deployment of Onyx into the cavernous sinus via a transvenous approach shows total occlusion of the fistula.
FIG. 2. Digital subtraction angiography of Case 2. Lateral (A) and anteroposterior (B) late phase arteriograms show a complex left indirect carotid-cavernous fistula (CCF) (arrow) fed from the left internal and external carotid arteries via petrosal and left inferior maxillary arterial branches. C. After Onyx occlusion of the left CCF (arrow), a right CCF is exposed (arrowhead). D. Arteriogram shows filling of the right CCF via branches of the right external carotid artery. E. The right cavernous sinus is accessed via a catheter in the superior ophthalmic vein. F. Lateral arteriogram shows complete closure of the right CCF by Onyx cast (arrow).

MTI Echelon-10 microcatheter. Post-Onyx views revealed closure of the complex left CCF (Fig. 2C). Screening time of this procedure could not be obtained because of imaging equipment failure at the end of the procedure. The patient had made a full clinical recovery by the time of discharge. The right fistula (Fig. 2D) was closed 3 months later using the same Onyx-34 technology. Because of the known occlusion of the inferior petrosal sinus, the right cavernous sinus was accessed via the right superior ophthalmic vein (SOV) using transorbital ultrasound guidance for catheterization of this vessel (Fig. 2E). The right cavernous sinus was closed using Onyx-34. Post-Onyx DSA views demonstrated successful closure of the fistula (Fig. 2F). Screening time was 23.7 minutes. There was some moderate postoperative conjunctival edema of the right eye, which was probably a result of the saline flushing of the right SOV. This resolved within 36 hours. The patient made a full recovery before discharge. Successful closure was confirmed on follow-up ophthalmic and MRI examination 3 months later.

Case 3
A 44-year-old woman presented with a 2-month history of severe headaches associated with nausea and vomiting in the morning. Pulsatile tinnitus, blurred vision of the left eye, and double vision on left gaze developed soon afterward. There was proptosis and conjunctival injection of the left eye, with diplopia on abduction. TR-MRA and DSA demonstrated a left CCF. The left cavernous sinus was accessed by advancing the Echelon-10 microcatheter through the right inferior petrosal sinus (IPS) and right cavernous and circular sinuses, and the fistula was successfully occluded using Onyx-34 (Fig. 3). Post-Onyx DSA views confirmed closure of the fistula. Screening time was 60.0 minutes. Ophthalmic and MRI review at 3 months after the procedure confirmed complete imaging closure and clinical recovery.

Case 4
A 64-year-old woman presented with a 6-month history of double vision on looking to the right. The right eye had also developed progressive reddening over the previous 4 months. There was conjunctival injection of the right eye without associated proptosis and diplopia on right gaze. MRA demonstrated a right type D CCF. It was successfully closed using Onyx-34 via the right IPS with an Echelon-10 microcatheter. Screening time was 39.1 minutes. The patient demonstrated complete reversal of symptoms and was discharged home the next day. The success of the treatment was confirmed on MRI and ophthalmic assessment 3 months later.

Case 5
A 64-year-old man presented with double vision on looking to the right. Arterialized conjunctival vessels were
FIG. 3. Digital subtraction angiography of Case 3. A. Lateral midphase right carotid arteriogram shows a complex left indirect CCF (arrow). B. An Echelon-10 microcatheter (arrow) deploys Onyx (arrowhead) into the left cavernous sinus via the right inferior petrosal sinus and right cavernous sinus. C. Lateral left carotid arteriogram shows complete closure of the complex left CCF (arrowhead).

present in the right eye. DSA confirmed the TR-MRA evidence of a right type D CCF. The fistula was successfully closed after embolization of the right cavernous sinus with Onyx-34 delivered via a right IPS approach with an Echelon-10 microcatheter. Screening time was 22.5 minutes. There was complete reversal in the patient’s symptoms postoperatively. Follow-up at 3 months with MRI and ophthalmic examination confirmed complete closure of the fistula and no return of ophthalmic symptoms.

The only possible complication among these patients was a temporary sixth nerve palsy in Case 1, which had resolved completely at the time of follow-up 3 months later.

DISCUSSION

We have reported successful closure without enduring complications of six Barrow type D CCFs in 5 patients using the Onyx Liquid Embolization System via a transvenous approach.

The major advantage of liquid systems such as the one we used is their ability to conform to irregular and complex vascular structures (11,13,14). However, these agents have historically been difficult to control owing to their liquid nature, which can render them dangerous because of the risks of occlusion of important vascular structures (11,13). The use of pure ethanol as a liquid embolization agent for endovascular procedures was first described by Yakes et al (17) in a series of 17 patients with cerebral vascular malformations. That series demonstrated the efficacy of the agent to cause vessel sclerosis but at the cost of a high complication rate, with 8 of 17 patients having significant neurologic deficits (11,17). Such high complication rates are in part a result of ethanol’s immediacy and reliability as a sclerosing agent, such that unwanted distribution of the agent resulted in cerebral infarction (11,17).

The next developmental stage involved the use of nBCA. This agent allows greater user-based control and thus has a reduced risk of cerebral infarction (12,13,18). Wakhloo et al (13) demonstrated this advantage in a series of 14 indirect CCFs in which angiographic and clinical cure was achieved with nBCA alone (n = 6) or in combination with coil embolization (n = 7) or polyvinyl alcohol (n = 1). Only one patient had spillage of an nBCA droplet into a cerebral vessel, a substantial improvement on the results of ethanol-based procedures (13). However, perforation of the inferior petrosal sinus during microcatheter placement was encountered in one patient as the result of catheter adhesion (12,13). The adhesion of microcatheters to the vessel wall with nBCA was also described by Debrun et al (19), who encountered 29 episodes of catheter adhesion in a series involving brain arteriovenous malformation embolizations.

The Onyx Liquid Embolization System has the ability to penetrate the complex network of vessels typical of indirect type D CCFs. In addition, it also has several properties that render it superior to other liquid-based systems such as pure ethanol and nBCA. Onyx is non-adhesive, maintains excellent penetrative ability for complex vascular structures, allows greater user-based control to reduce the risk of accidental embolization, and can be delivered via a single slow injection (11,12,13,16,20,21).

The use of Onyx to treat indirect CCFs was first described in a single indirect CCF by Arat et al (16) in 2002. This same team later demonstrated its successful use
in treatment of a superior sagittal sinus dural arteriovenous fistula (dAVF) (14). Suzuki et al (12) demonstrated the safe and effective use of Onyx in combination with detachable coils for the treatment of 3 indirect CCFs. Baccin et al (20) also described the use of Onyx in association with coils for the treatment of a single direct CCF. Before this report, no series of patients had been published in which the Onyx system was used as a single treatment technique for indirect CCFs, despite increasing theoretical and clinical evidence demonstrating its advantages over other liquid embolic systems.

The major drawback associated with the use of Onyx is the risk of retrograde penetration into the feeding arterial vessels of the fistula. This risk is particularly important in indirect CCFs when there is significant supply of the fistula by meningeal branches of the ICA, such as the inferolateral or meningohipophyseal trunks. Retrograde arterial penetration has been reported previously by Nogueira et al (22) in 12 intracranial dAVFs treated with Onyx as a single treatment technique. They noted that such retrograde penetration into arterial feeding systems had the potential to result in cerebral infarction, although this did not occur. Van Rooij et al (23) reported major cerebral infarctions as a result of such retrograde penetration in 2 of 44 patients with brain arteriovenous malformations (AVMs). Difficulty in visualizing the tiny arterial feeding vessels as they enter the cavernous sinus in indirect CCFs may allow accidental penetration of Onyx into the ICA, with the potential for cerebral artery embolization (22,23). The risk of this complication can be reduced by pausing the delivery of Onyx for several minutes when such reflux is visualized on fluoroscopy. The use of biplane fluoroscopy during Onyx injection will aid such visualization (22,23). In this series, we used Onyx-34 exclusively because of its higher viscosity to reduce the risk of such retrograde penetration. In addition, the diagnostic angiograms were closely studied beforehand for significant supply to the fistulas by inferolateral or meningohipophyseal trunks.

In this series we also described the use of a superior ophthalmic vein approach to the fistula (Case 2). This approach (2,8,21) is often necessary because there is a significant incidence of inferior petrosal sinus thrombosis, which interferes with access by that route.

This case series is limited by its low patient numbers, retrospective approach, and lack of a comparative cohort. As such, it is not possible to comment definitively on the overall safety and efficacy of the Onyx system in treatment of indirect CCFs via the transvenous approach. However, the excellent outcomes for patients in this series, increased control of agent delivery, reduced screening times, and lack of adhesive complications all indicate that there is great potential for the use of Onyx in the management of this condition.

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Successful Transarterial Embolization of a Barrow Type D Dural Carotid-Cavernous Fistula with Ethylene Vinyl Alcohol Copolymer (Onyx)

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Abstract: Endovascular occlusion via the transvenous route is the favored treatment method for dural carotid-cavernous fistulas (CCFs). Ethylene vinyl alcohol copolymer (Onyx), recently approved for treatment of arteriovenous malformations, has advantages over conventional liquid embolic agents in its nonadhesive nature, which allows for longer injections with decreased risk of catheter retention. We report the use of Onyx in the successful transarterial embolization of a dural CCF fed by arterial branches of the internal and external carotid arteries (Barrow type D) after multiple failed attempts to access the cavernous sinus transvenously. Transarterial Onyx embolization could be a valuable option in transarterial treatment of CCFs when venous access is difficult.


Dural-based carotid-cavernous fistulas (CCFs) are believed to result from dural sinus thrombosis (1). Also called indirect CCFs, they are distinct from direct CCFs (Barrow type A) that result from trauma or aneurysm rupture within the cavernous sinus (2). Dural CCFs are classified as type B, C, and D, depending on whether arterial feeders arise exclusively from the internal carotid artery (ICA) (type B), from the external carotid artery (ECA) (type C), or from both the ICA and ECA (type D) (3).

Endovascular occlusion, usually via a transvenous approach to the cavernous sinus, is the standard of care for symptomatic dural fistulas. A variety of embolic agents have been used, including detachable platinum coils, high-grade alcohol, and n-butyl cyanoacrylate (nBCA) (4). Recently, ethylene vinyl alcohol copolymer (Onyx; ev3 Neurovascular, Irvine, CA) has been successfully used in combination with detachable coils via the transvenous approach (4,5) and after covered stent placement in treatment of a recurrent dural CCF via the transarterial approach (6). We describe a case of a complex type D dural CCF that was successfully treated with transarterial embolization with Onyx after multiple failed attempts to catheterize the cavernous sinus.

CASE REPORT

A 70-year-old woman presented with sudden pain in the right eye, together with redness and proptosis of that eye. She had undergone a liver transplant and suffered chronic renal insufficiency, brittle diabetes mellitus, congestive heart failure, and severe iodine allergy.

Ophthalmologic assessment revealed best-corrected visual acuities of 20/70 in the right eye and 20/25 in the left eye. There was no afferent pupillary defect. Extraocular movements were full. Slit lamp examination showed modest chemosis and dilated, tortuous conjunctival vessels. Applanation intraocular pressures were 20 mmHg in the right eye and 15 mmHg in the left eye. Ophthalmoscopy disclosed retinal vein tortuosity and dot-blot hemorrhages in the right eye and no abnormalities in the left eye.

Given her complicated medical history, an angiographic evaluation was considered risky and a trial of observation and close follow-up was recommended. However, she experienced worsening visual acuity and orbital soft tissue swelling.

After receiving sodium bicarbonate infusion and oral n-acetylcysteine for prevention of contrast agent–induced nephropathy, she underwent a cerebral angiogram that demonstrated a Barrow type D CCF with multiple tiny arterial feeders from the ICA and ECA bilaterally (Figs. 1 and 2). Multiple dural arterial branches opacified a septated...
right cavernous sinus (Fig. 3). The ipsilateral inferior petrosal sinus (IPS) was occluded, and there was no filling of the left cavernous sinus. Venous drainage was via an enlarged right superior ophthalmic vein (SOV), which demonstrated two areas of stenosis, one involving the junction of the cavernous sinus and SOV and the other involving the junction of the SOV and the angular vein (Fig. 3).

Under general anesthesia, a standard transfemoral 5-F diagnostic catheter was placed in the right ECA for arterial contrast agent injections. A 6-F guide catheter was navigated via transfemoral venous access over a 0.035-inch glide wire into the origin of the ipsilateral jugular vein. Using an Echelon 10 (ev3 Neurovascular) microcatheter and Synchro 14 microwire (Boston Scientific), access could be obtained into the IPS, but it did not opacify the right cavernous sinus. We were equally unsuccessful in gaining access to the right cavernous sinus via the contralateral IPS. We then punctured the right facial vein, but could not advance the microcatheter beyond the junction of the angular and superior ophthalmic veins.

Next we exchanged the right ECA diagnostic catheter for a 5-F guide catheter (Envoy, Cordis, Miami) and superselectively catheterized the distal internal maxillary artery with an Echelon 10 microcatheter. The microcatheter was flushed with normal saline, and the catheter dead space was filled with dimethyl sulfoxide (DMSO). Onyx-18 was slowly injected into the microcatheter dead space over 1 minute. Using constant fluoroscopy and intermittent control angiography, the small branches of the terminal internal maxillary artery supplying the fistula were embolized. The Onyx cast finally penetrated and filled the septated portion of the cavernous sinus that harbored the fistula (Fig. 4). A total of 1.4 mL of Onyx-18 was injected over approximately 20 minutes. The microcatheter could be withdrawn easily after termination of Onyx injection. Postprocedure angiograms confirmed complete occlusion of the fistula (Fig. 5).
There were no immediate complications. The patient had a significantly improved appearance of her right eye on the day after the procedure. Visual acuity and ophthalmic congestive features improved over the next few days. At a 3-week follow-up visit, a left abduction defect was noted, consistent with a partial sixth cranial nerve palsy. At the 12-week follow-up visit, the abduction deficit had mostly resolved, and visual acuity was back to baseline. The orbital soft tissue edema had completely resolved.

DISCUSSION

We have demonstrated successful occlusion of a complex Barrow type D CCF with Onyx embolization via the transarterial route. A nonadhesive liquid embolic agent, Onyx received Food and Drug Administration (FDA) approval for embolization of intracranial arteriovenous malformations (AVMs) in July 2005, but it has recently also been used in the treatment of dural arteriovenous fistulas (7–9). One of its major advantages over nBCA is its nonadhesive nature, allowing for longer injections with decreased risk of catheter retention (8). Therefore, even fairly extensive and complex fistulas can be treated in one or two sessions (8,9). In our early experience (unpublished material), catheterization of a single large pedicle can allow Onyx penetration into the fistula and the draining vein, as well as retrogradely into the branches of other arterial feeders. This feature decreases the frequent need for superselective catheterization and embolization of different arterial feeders with the use of nBCA. Nogueira et al (9) found Onyx to be more predictable and controllable than cyanoacrylates.

Dural (indirect) CCFs are often supplied by tiny meningeal branches of the ICA and ECA that are difficult to catheterize superselectively. Therefore, transvenous occlusion of the cavernous sinus has been advocated as the mainstay of endovascular treatment because of its safety and high rate of permanent success (2,10,11). The goal of treatment is obliteration of the sinus and disconnection of the arteriovenous (AV) shunt, which can be accomplished with a variety of embolic agents.

Detachable platinum coils are the most commonly used agents, but sometimes these fail to completely occlude the sinus (12). Coil placement can also be limited by the complex architecture, septation, or small size of the affected cavernous sinus. This limitation has prompted several investigators to use nBCA as an embolic agent via the transvenous approach to the cavernous sinus (2,11). In our patient, however, it was impossible to navigate the microcatheter into the diseased cavernous sinus because of an occluded ipsilateral IPS, circular sinus, and high-grade stenosis at the junction of the SOV and angular vein. Although surgical exposure of the SOV was an option, this would have entailed significant prolongation of the procedure.

We were encouraged to use Onyx via the transarterial approach on the basis of our recent success with this agent in treating dural AV fistulas (unpublished data). A unique feature of Onyx is its ability to penetrate and travel along tiny arterial branches, ultimately allowing casting of rather remote venous pouches and occluding the fistula. This property is very helpful when the vascular tortuosity or small size of feeders prevents distal navigation of the microcatheter.
Arat et al (4) first described intracavernous injection of Onyx, in combination with coils, via an IPS approach. Subsequently, Suzuki et al (5) described the combined use of coils and Onyx in 3 patients. Lv et al (6) recently demonstrated transarterial Onyx treatment of a recurrent CCF that developed a dural supply; no complications were reported.

In our patient, a temporary contralateral abduction defect was noted at the 3-week follow-up. The cause of this complication is unclear, especially as there was no penetration of Onyx into the left cavernous sinus, but it could have been an inflammatory response generated by Onyx. Delayed cranial nerve palsy has been reported with the use of nBCA (2) and coils (13). Given that the existing clinical experience of treating CCFs with liquid embolic agents is relatively limited, continued caution and close follow-up are necessary.

One limitation of our report is the lack of angiographic follow-up. The complex medical history of our patient was a caution to follow-up angiography. However, previous animal studies have shown that the results obtained with Onyx are durable. No histologic evidence of recanalization was noted in a rete swine AVM model 6 months after Onyx embolization (14). Cognard et al (8) reported that among 23 of the 24 patients with dural fistulas treated with Onyx who underwent follow-up angiography at 3 months, none demonstrated recurrent fistulas.

A note of caution is necessary with the use of Onyx in the treatment of dural fistulas. Onyx has a propensity to retrogradely fill other arterial feeders to the fistula (9,15) either via their common connection to the vein or via preexisting collateral anastomoses. Therefore, thorough understanding of the morphology of the potential arterial feeders and the fistula is necessary before Onyx embolization is undertaken. The possibility of dangerous ICA-ECA anastomoses must always be kept in mind.

REFERENCES

Skew Deviation as the Initial Manifestation of Left Paramedian Thalamic Infarction

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Abstract: We describe a 73-year-old man who developed diplopia as the initial manifestation of a left thalamic infarction. By the time he reached the emergency department, clouded consciousness precluded localization of the lesion. Results of brain MRI were initially interpreted as negative. Ophthalmologic examination several hours later disclosed a small vertical ocular misalignment attributed to skew deviation. This finding led to careful scrutiny of the upper brainstem on MRI. Comparison of the diffusion, apparent diffusion coefficient, and exponential apparent diffusion coefficient MRI studies allowed a diagnosis of subtle left thalamic infarction. The recognition of skew deviation in this setting is important because it may be the most specific indicator of a brainstem lesion.

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The clinical manifestations of thalamic infarction depend principally on the region that has been injured (1). The thalamus is traditionally divided into four regions based on its arterial supply: anterior, paramedian, inferolateral, and posterior (2). The two most common infarcts involve the inferolateral thalamus, supplied by the inferolateral artery, and the paramedian thalamus, supplied by the paramedian (thalamosubthalamic) artery, a branch of the first segment of the posterior cerebral artery (P1). Less common are infarcts of the anterior thalamus supplied by the tuberthalamic artery and posterior thalamus supplied by the posterior choroidal arteries (2).

The principal clinical features of infarcts involving the paramedian thalamus—consisting of the medial dorsal nucleus, internal medullary lamina, and intralaminar nuclei—are decreased arousal, altered social skills and personality, short-term memory loss (amnesia), aphasia (with lesions on the left) or spatial deficits (with lesions on the right), vertical gaze paresis, impaired convergence, and skew deviation (2,3).

We describe a patient with infarction of the left paramedian thalamus who presented with vertical diplopia and later developed aphasia and amnesia. We emphasize that the paramedian thalamus is the only brain region in which a single lesion will produce this combination of deficits. The detection of skew deviation was challenging because of impaired consciousness but critical to early localization because the imaging abnormality was subtle.

CASE REPORT

A 73-year-old bilingual Japanese automotive executive who had resided in the United States for 20 years noticed vertical double vision upon awakening. He became progressively drowsy.

The patient’s medical history included supraventricular tachycardia, tachy-brady syndrome, benign prostatic hypertrophy, amebiasis, and peptic ulcer disease. Medications included fexofenadine (Allegra) and tamsulosin (Flomax). He was known to speak fluent English and had no history of hearing loss.

In the initial neurologic examinations in the emergency department 4 hours after symptom onset, examiners noted drowsiness without any focal neurologic deficits. Impaired consciousness precluded detailed neurologic examination. Results of brain CT (Fig. 1) and CT angiography were normal. Because of the report of diplopia, an ophthalmologic consultation was requested. Eight hours after symptom onset, the patient was sufficiently arousable to allow detection of a 4 prism-diopter right hypertropia with normal ocular ductions. There were no other ophthalmic abnormalities.

Thirteen hours after symptom onset, results of brain MRI were initially interpreted as normal. With the information that skew deviation had been detected, increased scrutiny of the upper brainstem region on MRI disclosed an area of restricted diffusion in the left paramedian thalamus, particularly when the diffusion, apparent diffusion, and exponential diffuse images were compared. The T2 and

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FIG. 1. Noncontrast axial CT performed 8 hours after symptom onset shows no abnormalities.

FLAIR MRI images through the equivalent section did not disclose any clear signal abnormality (Fig. 2).

Two days after hospital admission, he still had a 4 prism-diopter right hypertropia in primary gaze position. Consciousness had improved enough to permit ascertainment that he was disoriented to time and place. Speech-language evaluation disclosed that he was hypophonic but able to follow verbal single-step commands and repeat sentences such as “I got home from work.” He could not name visually displayed common objects such as a clock. He made frequent word substitutions with verbal paraphasic errors (“watch” for “clock”) more frequently than literal paraphasic errors (“buffon” for “button”). He could not complete automatic sequences, such as counting or carry out written commands, and his handwriting was small (micrographic).

On the fourth hospital day, he was fully awake. He could now verbalize automatic speech sequences, such as counting.

On the sixth hospital day, his motor speech, auditory comprehension for two-step directions, and ability to repeat longer sentences had improved, but he had persisting word-finding and reading comprehension deficits. He was discharged home with a therapeutic regimen of aspirin and atorvastatin.

On the eighth day after the stroke, a comprehensive outpatient speech and language evaluation was completed using portions of the Boston Diagnostic Aphasia Examination (BDAE) (4) and the Boston Naming Test (BNT) (5). The BNT specifically assesses visual confrontation naming and the ability to benefit from various probes. On these tests, he showed further improvement in motor speech production, the ability to follow verbal one-step and two-step commands, and intact sentence repetition, but scored only 8 of 60 on the BNT, more than 4 SD below the mean. He still had reading comprehension deficits at the single-word level but was responding to cueing.

Fourteen days after stroke onset, the hypertropia was restricted to up-and-right gaze. There were no other neurologic deficits except disorientation to time and a lingering aphasia.

Twenty-one days after stroke onset, he still had deficits in word-finding. As his language skills resolved, it became apparent that he had difficulties in short-term memory and in executive dysfunction, including impaired awareness of his deficits and reduced ability to set goals and to plan and organize his professional tasks (Table 1).

One year after the stroke, he still had lingering hypertropia, but informal examination of mental status and language disclosed no deficits. He had returned to work and acknowledged no memory or other cognitive deficits.

FIG. 2. MRI performed 13 hours after the initial onset of symptoms. A. Axial diffusion image through the paramedian thalamus shows subtle high signal (arrow). B. Axial apparent diffusion coefficient map through this level shows low signal in the same location (arrow), consistent with restricted diffusion. C. Axial exponential apparent diffusion coefficient map shows corresponding high signal (arrow), making this focus of restricted diffusion quite conspicuous. D. T2 axial image through the paramedian thalamus shows no definite focal signal alteration (arrow). E. Axial FLAIR image through the paramedian thalamus shows subtle signal inhomogeneity but no definite focal signal alteration (arrow).
TABLE 1. Evolution of aphasic deficits in our patient

<table>
<thead>
<tr>
<th>Day</th>
<th>Hypophonia</th>
<th>Auditory Comprehension</th>
<th>Sentence Repetition</th>
<th>Spontaneity of Oral Expression</th>
<th>Verbal Paraphasias</th>
<th>Jargon Speech</th>
<th>Word-Finding Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2</td>
<td>Moderate-severe</td>
<td>One-step verbal commands</td>
<td>Limited to high probability sentences</td>
<td>Severely nonfluent</td>
<td>Frequent</td>
<td>None</td>
<td>Severe</td>
</tr>
<tr>
<td>Day 6</td>
<td>Mild</td>
<td>One- and two-step verbal commands</td>
<td>Limited to high and some low probability sentences</td>
<td>Moderately nonfluent</td>
<td>Occasional</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td>Day 8</td>
<td>Very mild</td>
<td>Two-step verbal commands</td>
<td>Intact</td>
<td>Mildly nonfluent</td>
<td>Rare</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td>Day 21</td>
<td>None</td>
<td>Intact</td>
<td>Intact</td>
<td>Fluent</td>
<td>Rare</td>
<td>None</td>
<td>Mild</td>
</tr>
</tbody>
</table>

DISCUSSION

Our patient presented with acutely impaired consciousness, vertical ocular misalignment, aphasia, and amnesia caused by left paramedian thalamic infarction. CT results were negative, and MRI showed only a subtle area of restricted diffusion that was initially overlooked. The report of diplopia as the initial symptom called forth an ophthalmologic examination, which led to the detection of a small vertical ocular misalignment attributed to skew deviation. That finding directed attention to the brainstem, which led to a reevaluation of the MRI. Once the diffusion images were studied carefully and matched with apparent diffusion coefficient (ADC) and exponential apparent diffusion coefficient (eADC) maps, the small paramedian thalamic infarction was recognized. It was only after consciousness improved that language and memory deficits characteristic of lesions in this region were recognized.

Skew deviation has been reported in thalamic infarction (3,6–10), but not as often as vertical gaze paresis (1–3,7,11–14). Our patient is unusual in having reported diplopia as an early symptom and in having skew deviation without other ocular motor abnormalities. Skew deviation rather than vertical gaze paresis probably occurs when the infarct is relatively small and the peri-infarct edema extends minimally into the rostral midbrain tegmentum in the territory of the medial longitudinal fasciculus and the interstitial nucleus of Cajal (6,15).

Skew deviation was described by Dieterich and Brandt (6) in 8 of 14 patients with unilateral paramedian thalamic infarction. In addition to vertical ocular misalignment, these patients had a head tilt opposite to the side of the lesion, ocular torsion, and subjective visual vertical tilt. We did not assess these features in our patient because head tilt was not present.

Among 40 patients with thalamic infarction, Bogousslavsky et al (7) listed skew deviation in only 1, a patient who had a unilateral paramedian lesion. No further details of ocular alignment testing were provided. A report of 2 patients with combined polar-paramedian thalamic infarcts (one on the left and one bilateral) mentioned skew deviation as a feature in both, but no details of the neuroophthalmic examination were included (3). A single case report of bilateral paramedian infarction confined to the thalamus described an ocular tilt reaction as the only manifestation (9). The authors reported hypertropia and ocular torsion present on fundus photography. Transient vertical diplopia without ocular ductional deficits was reported in a patient with unilateral ventrolateral thalamic infarction; nystagmus was the only other finding (10).

Skew deviation also occurs in thalamic hemorrhage. In a prospective study of 100 patients with thalamic hemorrhage (16), the authors reported skew deviation in 17 (31%) of the 55 patients in whom the lesion was posterolateral. A case report of bilateral thalamic hemorrhage described a patient with tetraplegia and skew deviation but no details of the ophthalmic examination were provided (17). Transient skew deviation in thalamic infarction and hemorrhage may be more common than reported, considering that impaired consciousness could interfere with its detection (8,18,19).

During the period of reduced consciousness, language deficits are often noted, as in our patient. There is debate as to whether these language deficits represent a true aphasia or whether they are caused by impaired arousal, attention, and motivation. In our patient, however, the language deficits appeared to meet the criteria for a limited aphasia (20–23). They included word-finding errors, frequent word substitution, and paraphasias (related-word substitutions) with minimally impaired repetition and no auditory comprehension deficits. These deficits resemble transcortical motor aphasia but are distinctive in having more frequent paraphasic errors (24), rapid resolution of speech and language deficits, and lingering executive...
cognitive and short-term memory loss (3). The similarity between thalamic and transcortical motor aphasias suggests that the linguistic role of the thalamus is related to its connections to the frontal lobe anterior to Broca’s area and to the tempo-parietal-occipital junction posterior to Wernicke’s area (25). As expected, our patient showed relatively rapid recovery of consciousness and language skills (3).

As consciousness and language improved, significant lingering deficits in memory and executive function became evident (26–28). These deficits may be explained by the fact that thalamic nuclei have extensive reciprocal connections with the cerebral cortex, particularly between the frontal lobes and dorsal medial thalamus (28,29). That such deficits may have more long-term adverse effects than the language problems was borne out in our patient, who had protracted difficulty resuming his position as an automotive company executive.

Our patient demonstrates the fact that small thalamic infarcts may have potent neurologic effects yet subtle imaging findings. Although CT is very helpful in the emergency imaging evaluation of suspected brain infarction because of its rapid image acquisition and its sensitivity in the detection of acute hemorrhage, nonhemorrhagic infarcts often do not show detectable differences in attenuation until many hours after the event. MRI is much more sensitive in the detection of ischemic or infarcted brain tissue, especially when diffusion imaging is performed (30). By isolating the diffusion coefficient, it is possible to obtain an idea of the properties of diffusion occurring within a particular voxel. These values, called ADCs, can then be mapped as an image, using diffusion as the contrast. By using further cancellations, exponential maps, called eADCs, can be generated. The comparison of diffusion imaging and ADC maps has notably improved sensitivity and specificity, particularly with the addition of eADC. Although the combination of diffusion imaging and ADC maps often suffices to be certain of restricted diffusion, at times artifacts appear on ADC maps (30). The addition of eADC maps helps to cancel such artifacts and increase certainty in cases of subtle restricted diffusion (30). Diffusion imaging, ADC maps, and eADC maps must be compared to obtain the most certain results. Foci of true restricted diffusion will show increased signal on diffusion imaging and eADC maps and low signal on ADC maps.

REFERENCES

Periodic Alternating Nystagmus and Periodic Alternating Skew Deviation in Spinocerebellar Ataxia Type 6

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Abstract: The combination of periodic alternating nystagmus (PAN) and periodic alternating skew deviation (PASD) is rare. We report a case of PAN and PASD in a patient with spinocerebellar ataxia type 6 (SCA-6) and discuss the role of the cerebellum as a plausible mechanism for this combined pathologic condition.

Various conditions have been reported to cause combined periodic alternating nystagmus (PAN) and periodic alternating skew deviation (PASD), including brainstem abscess (1), multiple sclerosis (MS) (2), degenerative vascular disease, vertebral artery compression (3), midbrain infarction (4), and iatrogenic vermian biopsy causing injury to the uvula (5). PAN without PASD has previously been reported to occur with spinocerebellar ataxia type 6 (SCA-6) (6). We have found only one other reported case of a patient with combined PAN and PASD (7); that patient had presumed hereditary cerebellar ataxia but no specific genetic diagnosis. Combined PAN and PASD have not been reported in the clinical setting of a genetically confirmed spinocerebellar ataxia syndrome. This association would strengthen the argument that cerebellar dysfunction is a focal point in the pathogenesis of PAN and PASD.

CASE REPORT
A 58-year-old African-American man presented with worsening vision over at least 6 months. He had progressed to wheelchair dependence over 6 years because of worsening ataxia. He had developed severe extremity tremors and dysarthria. His family history suggested the presence of a “balance problem” in his father and a paternal uncle but neither had a genetic diagnosis, and the patient had lost contact with his family. He had two sons who were reportedly neurologically normal. In an earlier evaluation in a movement disorders clinic, molecular genetic testing had shown an expansion on the SCA-6 gene of 22 repeats, confirming a diagnosis of SCA-6. A recent MRI had shown only pancerebellar atrophy, which was unchanged.

Neuro-ophthalmologic examination showed a best-corrected visual acuity of 20/100 in both eyes. Confrontation and Goldmann visual fields were normal. Pupils were normal. He had full versions but markedly impaired smooth pursuit and dysmetric saccades. He had PAN with a cycle of about 120 seconds and a right-beating nystagmus, a still period of about 10–15 seconds, and then a left-beating nystagmus. The cycle repeated itself through the examination. He also had a periodic alternating hypertropia, typically a left hypertropia when the nystagmus was right-beating and a right hypertropia when the nystagmus was left-beating. The duration of the hypertropia would vary between cycles and did not follow a rhythmic pattern. Intraocular pressures were normal. Slit-lamp examination revealed mild nuclear cataracts. Ophthalmoscopy was normal. The visual acuity loss was attributed to oscillopsia, and low-dose baclofen was started, which produced improvement in oscillopsia. He was then lost to follow-up.

DISCUSSION
We report here the first case of combined PAN and PASD in a patient with genetically confirmed SCA-6. The combination of PAN and PASD is itself quite rare, and the association with a specific, well-characterized cerebellar ataxia lends insight into the pathophysiology of PAN and PASD.

Skew deviation is a vertical misalignment of the eyes caused by damage to prenuclear vestibular input to the ocular motor nuclei. When it occurs on an interchanging
cyclic basis, the abnormality is called PASD. Acute hydrocephalus, tumors, strokes, and MS are the most frequent causes of PASD, followed by spinocerebellar degeneration and tentorial herniation (8). PAN, a spontaneous conjugate nystagmus that involves regular cycles of "active" and "quiet" phases, has a differential diagnosis similar to that for PASD (5). A cycle of PAN includes a left-beating nystagmus, a quiet or transitional phase, a right-beating nystagmus, and a second transitional phase.

SCA-6 is a progressive, degenerative, autosomal dominant condition resulting in late-onset adult cerebellar ataxia, dysarthria, and ocular motor disorders such as nystagmus (9,10). It is characterized by trinucleotide CAG expansions occurring within the gene CACNA1A on chromosome 19p13, which encodes for the \( \alpha_1 \) voltage-dependent subunit of the calcium channel (11). In SCA-6, the most affected calcium channels are of the Cav2.1 p-type, a subtype most prominent within the cerebellar Purkinje cells (12). The dramatic Purkinje cell loss and dysfunction that results from SCA-6 occurs predominantly within the vermis, flocculus, nodulus, and uvula (13,14). This preferential involvement of cerebellar structures could explain a predisposition to the rare concurrence of PAN and PASD. Radtke et al (5) described PASD in a patient who underwent biopsy of the inferior cerebellar vermis, resulting in destruction of the uvula.

The periodic rhythmic ocular oscillation of PAN has been associated with various cerebellar disorders and has been attributed to an instability or increased gain in the vestibulo-ocular reflex (VOR) (9,15). The VOR circuit is regulated by three main components: Purkinje fibers from the archicerebellum, mossy fibers from the pontine nucleus, and the interstitial nucleus of Cajal (vertical integrator in the midbrain) (16). The cerebellar nodulus and uvula are essential in habituating and stabilizing the VOR. Selective ablation of these areas has resulted in PAN (5). The VOR model postulates neuroelectric relays that conduct information regarding head position from the otolith organs and semicircular canals to the contralateral sixth cranial nerve nucleus and ipsilateral third cranial nerve nucleus, eventually stimulating the contralateral lateral rectus and the ipsilateral medial rectus to stabilize images on the retina during head movement. However, stability of the VOR depends on cerebellar sampling of this information.

The mechanism of PASD is unknown but may involve pathways from both utricles to the vertical-rotatory ocular motor neurons, loss of cerebellar control of vertical vergence, or both. Once thought to be associated only with brainstem lesions and extensive cerebellar destruction, skew deviation has now been described with a localized lesion in the ventral caudal portion of the vestibular complex (17). PASD has previously been described in a patient with presumed hereditary cerebellar degeneration (18) in a report predating molecular genetic testing, so the specific syndrome was not identified.

The combination of PAN and PASD in spinocerebellar ataxia might be under-reported owing to lack of an accurate diagnosis. Hereditary spinocerebellar ataxias should be considered as part of the differential diagnosis of patients with this finding. Careful examination of these patients might refine the anatomical definition of otolith-ocular pathways. Clinicopathological study of discrete cerebellar lesions associated with skew deviation should help resolve the causative role of the cerebellum in skew deviation.

REFERENCES

Spontaneous Intracranial Hypotension Presenting as a Reversible Dorsal Midbrain Syndrome

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Abstract: A 47-year-old woman with postural headache, episodic stupor, and vertical gaze palsy had brain imaging findings consistent with spontaneous intracranial hypotension (SIH), including severe descent of the mesodiencephalic structures and diffuse pachymeningeal enhancement. The source of the cerebrospinal fluid leakage was a ruptured dorsal perineural cyst. Clinical symptoms improved after a targeted epidural blood patch was performed. Dorsal midbrain syndrome has not been reported previously as a manifestation of SIH. Perhaps distortion of structures in this brain region can occur in SIH as it does in obstructive hydrocephalus.

(CASE REPORT)

A 47-year-old woman was admitted to the hospital with a severe bifrontal throbbing headache associated with dizziness and vomiting. Two weeks before admission, the patient had noticed that the headache was accentuated in the upright position and was partially relieved in the recumbent position. The patient suffered brief episodes of lethargy associated with gait ataxia and difficulty looking down. She had a history of breast cancer with no evidence of recurrence or metastatic disease.

There were no meningeal signs or fever. Mild bilateral lid retraction was noted. Pupils were symmetrical and demonstrated light-near dissociation, with no constriction to light but a slight constriction when viewing a target at reading distance. Horizontal eye movements were normal, but there was loss of voluntary upgaze and downgaze pursuit and saccadic movements, with partial preservation of reflex vertical eye movements provoked by the oculocephalic maneuver. Convergence was impaired. There was no nystagmus. She did not complain of diplopia, and cover testing did not identify a misalignment. Papilledema was not detected. The remainder of the neurological examination was unremarkable.

Results of serum biochemistry analysis, a full blood count, coagulation tests, and serologic tests for syphilis and HIV were negative. Electroencephalography (EEG) showed no abnormalities. Results of a brain CT scan were normal. After a prolonged period of sitting up, she developed severe headache, decreased consciousness, dystonic posturing of the arms, and slow conjugate horizontal ocular oscillations (20–25 amplitude and 0.5 Hz frequency).

Brain MRI (Fig. 1) disclosed generalized downward displacement of the midline structures with severe flattening of the midbrain and pons. Postcontrast T1 axial images demonstrated mild diffuse pachymeningeal enhancement. Diffusion MRI and MRA showed no abnormalities. Lumbar puncture and CSF pressure measurement was normal.

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FIG. 1. Brain MRI performed at the time of findings of dorsal midbrain syndrome. A. Precontrast T1 sagittal image shows descent of the brain and cerebellar tonsils, effacement of the prepontine cistern, and an enlarged pituitary gland. B. Postcontrast T1 axial image shows abnormal pachymeningeal enhancement. C, D. Axial T2 images show compression of the pontomesencephalic junction (C) and at the tentorial incisura (D) with no intraparenchymal signal abnormality. These features are typical of spontaneous intracranial hypotension.
not performed because of concern about the safety of CSF removal in this clinical context.

The patient was transferred to another inpatient setting where spine MRI and radioisotope cisternography confirmed a CSF leak at the T11–12 level. An epidural blood patch was performed.

One month later, our examination documented full recovery of vertical eye movements, convergence, and pupillary constriction to light. Three months later, orthostatic headache recurred but was unassociated with eye movement abnormalities or altered consciousness. An epidural blood patch was repeated without relief of symptoms.

A follow-up MRI performed 3 months later and not available for our review reportedly showed mild elevation of the cerebellar tonsils and better visualization of the prepontine cistern. Over a follow-up period of 7 years, the patient continued to demonstrate normal eye movements and convergence.

DISCUSSION

SIH is a rare condition caused by spinal CSF leakage. The resulting low CSF pressure and volume have two main pathophysiological consequences: a compensatory increased cerebral venous volume and descent of the brain due to a reduction in the supportive buoyant action of the CSF (5). The latter phenomenon tends to occur when other compensatory mechanisms have been exhausted and may explain some of the atypical patterns of clinical presentation associated with SIH. These patterns include diplopia, ataxia, fluctuating conscious state, and parkinsonism (2,6–8).

In the present case, the diagnosis of SIH is supported by postural headache, typical neuroimaging findings, and the initial response to an epidural blood patch. Lumbar puncture is not necessary for establishing the diagnosis, as the opening CSF pressure can be normal and may exacerbate the symptoms (2).

A reversible dorsal midbrain syndrome has not been previously associated with SIH. The classic features of this syndrome include a limitation of upgaze with relatively preserved vestibular and oculocephalic reflexes, convergence-retraction nystagmus on attempted upgaze, and eyelid retraction (9). The pupils may be normally reactive, although light-near dissociation has been well described (10). This patient was slightly atypical in that she had a vertical gaze palsy affecting voluntary eye movements in upgaze and downgaze, suggesting impairment of tegmental midbrain function.

Dorsal midbrain syndrome most commonly occurs in the presence of ischemia or tumors, although it may also occur with obstructive hydrocephalus (11). In these cases, dorsal midbrain dysfunction due to raised intracranial pressure has been postulated as the mechanism, supported by patients in whom the manifestations have resolved after the increased intracranial pressure was relieved (12). The sensitivity of this region to mechanical distortion, whether caused by high or low intracranial pressure, suggests that a causal association between SIH and the dorsal midbrain syndrome is biologically plausible. Presumably, the dorsal midbrain becomes distorted as the brainstem is no longer suspended and supported in its CSF jacket.

In our patient, we hypothesize that the midbrain displacement induced by the SIH led to stretching of structures involved in the control of vertical eye movements, including the rostral interstitial nucleus of the medial longitudinal fasciculus (rMLF), the interstitial nucleus of Cajal (INC), the posterior commissure (PC), and the nucleus of the posterior commissure (nPC) (13). Vertical gaze palsy and intermittent unresponsiveness have been described in patients with lesions affecting the thalamus and midbrain in the area corresponding to the rMLF (14). We postulate that the impairment of downgaze as well as upgaze implies involvement of the rMLF. Concomitant involvement of the PC and nPC or their projections must also have occurred.

We suggest that the pathophysiological mechanism for involvement of these structures in SIH is similar to that postulated for the occurrence of a dorsal midbrain syndrome in obstructive hydrocephalus, in which an enlargement of the aqueduct or third ventricle results in stretching or compressing of the PC. Altered mental status is an unusual complication of SIH (7,15). Our patient presented with recurrent stupor and areflexic pupils. Clinical and pathological studies have shown that the midbrain and pontine areas critical to consciousness in humans lie in the paramedian tegmental zone immediately ventral to the ventricular system and continue rostrally to the posterior hypothalamic area. Bilateral lesions of the ventromedial thalamus have been reported in patients with recurrent episodes of stupor (14). The reduced consciousness and ocular motility abnormalities may have been related to diencephalic and rostral midbrain compression due to severe brain descent.

Based on this case, we suggest that the clinical spectrum of SIH be broadened to include a dorsal midbrain syndrome. Prompt diagnosis is essential to avoid potentially serious consequences.

REFERENCES

Ocular Dipping in Creutzfeldt-Jakob Disease

Seong-Hae Jeong, MD, SangYun Kim, MD, Seong-Ho Park, MD, and Ji Soo Kim, MD

Abstract: Ocular dipping refers to a slow downward deviation of both eyes followed by a quick return to the midposition after a brief delay. Two patients with rapid neurologic deterioration in Creutzfeldt-Jakob disease (CJD) displayed ocular dipping, which quickly evolved into sustained downgaze deviation. Ocular dipping may thus be a transitional sign in a vertical gaze disturbance.


Creutzfeldt-Jakob disease (CJD) is characterized by rapidly progressive dementia, myoclonus, and ataxia (1). Involuntary eye movements in CJD include periodic alternating, upbeat, centripetal, and rebound nystagmus (2–4). As the disease progresses, saccadic slowing, supranuclear vertical gaze palsy, and periodic alternating gaze deviation may develop (2,4). Eventually, all saccades, including quick phases of nystagmus, are lost.

We report transient ocular dipping (inverse bobbing) that evolved into downgaze deviation in 2 patients with CJD. This is the first report of ocular dipping in CJD and its link to downgaze deviation.

CASE REPORTS

Case 1

A 47-year-old man reported that people appeared to him as aliens. His acquaintances had begun to notice that he did not recognize them as he did not greet them. Over the following weeks, he began to bump against his surroundings as if he were blind. His wife noticed severe deficits of memory and executive function. His past medical history was unremarkable. He did not take any medication.

On admission to our hospital, vital signs and general examination findings were normal. However, he showed psychomotor slowing, anoma with preserved fluency, ideomotor apraxia, right-left disorientation, finger agnosia, agraphia, and acalculia. He failed to copy simple figures such as interlocking pentagons. All three components of Balint syndrome—ocular apraxia, optic ataxia, and simultanagnosia—were present, as well as color agnosia. He could not follow a visual target, and vertical and horizontal saccadic eye movements appeared to be slow.

A lumbar puncture showed clear cerebrospinal fluid (CSF) with an opening pressure of 100 mm H2O, 15 red blood cells, 0 polymorphonuclear cells, 142 mg/dL protein, and 91 mg/dL glucose (blood glucose, 87 mg/dL). CSF 14-3-3 protein was positive. Routine chemistry values, syphilis serology, and thyroid function were unrevealing. Electroencephalography (EEG) demonstrated continuous 4–6 Hz irregular mixed slowing in all leads. Diffusion MRI revealed high signal abnormalities in the caudate and putamen, left frontal cortex, and bilateral occipitotemporal and insular areas (Fig. 1).

On the second hospital day, he began to deteriorate rapidly, showing confusion and intermittent violent behavior. He was akinetic between the violent episodes. He was unable to open his eyes voluntarily or follow simple commands and showed intermittent myoclonus in the fingers and hands. Doll’s eye movements were full in all directions. The pupils were equal at 3 mm and normally reactive to light. When his eyelids were held open by the examiner, a slow downward deviation of both eyes was followed by a quick return to the mid position after a brief delay, a finding considered consistent with ocular dipping. The ocular dipping clustered for 6–10 seconds; two or three cycles would occur in succession at intervals of 3–10 seconds. Subtle upbeat nystagmus appeared to be intermixed. There was no phasic contraction of the orbicularis oculi muscle. The ocular dipping lasted a few days and changed to sustained downward gaze deviation.

Genetic analyses of the prion protein gene using blood demonstrated a homozygosity for methionine at the codon 129 polymorphic site on the short arm of chromosome 20. The family members declined brain biopsy. The patient was discharged and lost to follow-up.

Case 2

A 67-year-old journalist had a 1-month history of facial paresthesias and slurred speech that had started after
a quarrel. Two weeks before admission, he experienced unsteadiness and became unable to walk without support. He also had swallowing difficulties.

On admission, he was alert and fully oriented. However, he showed spontaneous upbeat nystagmus, horizontal gaze-evoked nystagmus, and slow saccades. Upbeat nystagmus increased during upgaze, convergence, lying down, straight head hanging, and Hallpike maneuvers. Volitional eye movements were full in all planes.

Although results of diffusion MRI 20 days earlier had been normal, follow-up imaging showed subtle high signal intensities in the left caudate nucleus, anterior putamen, insular cortex, and precentral and postcentral gyri, and bilateral medial parietal cortex (Fig. 2). [(18F)Fluorodeoxyglucose positron emission tomography (PET) of the brain showed hypometabolism in the areas corresponding to the MRI lesions. CSF 14-3-3 protein was positive. EEG showed diffuse slowing.

Over the next 2 weeks, the patient deteriorated into a vegetative state with intermittent twitching of the extremities. Along with the spontaneous upbeat nystagmus, the patient showed ocular dipping, which was present only for a few days and evolved into downward gaze deviation and then horizontal periodic alternating gaze deviation.

Genetic analyses of the prion protein gene using blood demonstrated homozygosity for methionine at the codon 129 polymorphic site on the short arm of chromosome 20. The patient was discharged without further workup including brain biopsy and was lost to follow-up.

DISCUSSION

Although pathologic confirmation was unavailable in our patients, the clinical, laboratory, genetic, and imaging findings were consistent with CJD (5). Case #1 presented...
with isolated visual symptoms that are characteristic of the Heidenhain variant of CJD (6). In contrast, Case #2 initially developed severe ataxia and dysphagia. Examination revealed upbeat and gaze-evoked nystagmus, which are consistent with the ataxic form of CJD (7). Both patients rapidly lapsed into a bedridden or vegetative state over a few weeks.

Our patients showed upbeat and gaze-evoked nystagmus, downward gaze deviation, slow saccades, and ocular dipping. Although other ocular motor findings developed early in the course of the disease, ocular dipping was observed after marked deterioration of the patients' conditions.

Ocular dipping consists of an initial slow downward movement of the eyes and a following rapid return to the primary position (8). It occurs most often in hypoxic or metabolic encephalopathy (9–13). In contrast to ocular bobbing, which consists of a rapid downward movement of the eyes followed by slow return to the primary position and is generally regarded a sign of intrinsic pontine lesions (14,15), ocular dipping does not have localizing value and usually indicates diffuse brain dysfunction (8–10). Ocular dipping also should be differentiated from reverse and converse bobbing. Reverse bobbing consists of an initial jerk upward movement and a slow return to the mid position after a brief delay (16). Converse bobbing (also called “reverse dipping”) consists of an initial slow upward gaze deviation followed by a rapid return to the mid position (14).

Diffuse hypometabolism on brain PET in one of our patients and the development of ocular dipping in the advanced phase of the disease also support the notion that diffuse cerebral dysfunction is required to develop ocular dipping. In patients with ocular dipping, previous studies have reported diffuse pathologic changes in the basal ganglia, cerebral cortex (including the hippocampus), and cerebellum (9,12). The neuropathologic changes of CJD have been observed in similar areas, including the neocortex, thalamus, basal ganglia, and cerebellar cortex (3,17).

Previous reports on eye movements in CJD were mostly of patients with the ataxic (cerebellar) form of the disease. Periodic alternating nystagmus and slow vertical saccades appearing early in the course of CJD suggest involvement of the cerebellar nodulus and ventral uvula and the brainstem reticular formation (2,7). Case #2 presented with severe imbalance along with upbeat and gaze-evoked nystagmus, which suggests cerebellar dysfunction. The evolution of ocular dipping into sustained downgaze in our patients also indicates a complete loss of upward saccades (18,19). Ocular dipping may thus be a preliminary phase of downward gaze deviation. Development of periodic alternating gaze deviation in the later stage of the disease is explained by progressive loss of saccades and quick phases of nystagmus (20).

In our two patients, ocular dipping developed after marked deterioration in neurologic function and lasted only a few days before evolving into downgaze deviation. Ocular dipping in CJD presumably indicates an advanced stage of this devastating disorder.

REFERENCES
Binocular Vertical Rectus Muscle Recession
For Comitant Vertical Strabismus

Oliver Bergamin, MD, Maria Gabriela Wirth, MD, and Klara Landau, MD

Background: Binocular vertical rectus muscle recession has not been formally evaluated in the correction of comitant vertical strabismus.

Methods: Eight patients with stable comitant vertical strabismus for at least 6 months were included. All underwent recession of the superior rectus muscle of the hypertropic eye combined with an equal or nearly equal recession of the inferior rectus muscle in the hypotropic eye. On the day before surgery, on one of the first three postoperative days, and at one year postoperatively, ocular alignment in vertical and horizontal gaze directions were measured with simultaneous and alternate cover test at a viewing distance of 5 meters, and with the two dimensional Hess screen test. The field of single binocular vision was determined with a Goldmann perimeter. The Lang stereopsis chart was presented at the last follow-up visit.

Results: All patients were orthotropic at the last postoperative follow-up visit. In primary gaze, the degree of vertical and horizontal phoria diminished significantly. Normal alignment was achieved in nearly all gaze directions and stereopsis was reestablished. The field of single binocular vision enlarged after the surgery.

Conclusions: Binocular vertical rectus muscle recession is an effective surgical approach for patients with comitant vertical ocular misalignment.


The correction of vertical ocular misalignment poses a special challenge. There is less fusional amplitude in vertical than in horizontal misalignment because vertical misalignment is minimally influenced by vergence and other mechanisms of fusion. Vertical eye misalignment is often incomitant. However, spread of comitance may develop even in paretic or restrictive vertical strabismic forms when the innervation pattern of the unaffected muscles is adjusted to compensate for the impaired component of the ocular motor plant (1).

Although prisms provide symptomatic improvement, especially in misalignments of up to 10 prism-diopters (2), larger comitant vertical misalignments are usually managed by vertical extraocular muscle surgery. In this study we examine 8 patients whose comitant vertical misalignment was treated by recession of the superior rectus muscle of the hypertropic eye combined with an equal or nearly equal recession of the inferior rectus muscle in the hypotropic eye (binocular vertical rectus muscle recession).

METHODS

Subjects
Between December 1991 and August 2002, all patients with nonrestrictive comitant or nearly comitant vertical strabismus were treated with binocular vertical rectus muscle recession at the Orthoptic Unit of the Department of Ophthalmology, Zurich University Hospital. Eleven subjects (1.04%) were recruited consecutively out of the 1,065 patients who had strabismus surgery during the study time period. Institutional review board/ethics committee approval was not required for this retrospective study. Three patients were excluded either because the preoperative vertical incomitance between 15° right and 15° left gaze was >10° using the Hess screen test, the difference in recession between the right and the left eye was >1 mm, or a horizontal extraocular muscle was also operated upon. The remaining 8 patients included 3 men and 5 women, with a mean age of 34 years and a range of 9-56 years. The underlying diagnosis and the side of the hypertropic eye are shown in Table 1. Preoperatively all patients reported intermittent or constant double vision. Detection of stereoacuity with or without prism correction provided evidence of normal retinal correspondence. Forced duction testing revealed no limitation of passive ocular motility in either eye.
TABLE 1. Clinical features of 8 patients with comitant vertical strabismus

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Preoperative Vertical Misalignment with Alternate Cover Test</th>
<th>Recession (mm) of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Left HT 12 PD</td>
<td>Superior Rectus</td>
</tr>
<tr>
<td>1</td>
<td>Old right orbital floor fracture</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Long-standing thyroid orbitopathy</td>
<td>Right HT 25 PD</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Long-standing thyroid orbitopathy</td>
<td>Right HT 14 PD</td>
<td>3, 3.5</td>
</tr>
<tr>
<td>4</td>
<td>Old right orbital floor fracture</td>
<td>Right HT 25 PD</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Old left orbital floor fracture</td>
<td>Left HT 14 PD</td>
<td>2.5</td>
</tr>
<tr>
<td>6</td>
<td>Old traumatic brain injury, skew deviation?</td>
<td>Left HT 12 PD</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>Old acquired left trochlear nerve palsy</td>
<td>Left HT 20 PD</td>
<td>2.5</td>
</tr>
<tr>
<td>8</td>
<td>Congenital left trochlear nerve palsy</td>
<td>Left HT 16 PD</td>
<td>3</td>
</tr>
</tbody>
</table>

HT, hypertropia; PD, prism-diopters.

Data Analysis

Ocular misalignment was measured in prism-diopters with the simultaneous and alternate prism and cover test for distance fixation. The degree of misalignment was also determined in 15° left, straight ahead 15° right gaze, 15° upgaze, and 15° downgaze directions using the Hess screen test. Data were predominantly obtained on the day before surgery (pre-OP), at one of the first 3 postoperative days (post-OP), and at various times after surgery (1-year follow-up), (range 3–17 months, median 12 months follow-up).

The field of single binocular vision (diplopia-free zone) was determined with Goldmann stimulus size 5 (1.68° diameter) on the Goldmann perimeter (Haag-Streit, Bern, Switzerland). The patients pressed a button when a stimulus that was moved toward the center of the bowl appeared single instead of double. The fields of single binocular vision were all copied on paper with the same weight. To determine the size of the diplopia-free zone, this area was cut with scissors and weighed on a Mettler Toledo PG 503-S Delta Range scale, scaled in milligrams. The weight was calibrated with circular fields of radius 10, 20, 30, 40, 50, and 60°. No fields of single binocular vision were obtained from Case 3 and 6. In Case 7, this test was only performed at the post-OP and the 1-year follow-up visit. At the preoperative visit of Case 7, diplopia was present in all gaze directions, and therefore the value was set to zero.

To investigate the change in torsional alignment separately from the horizontal and vertical components of misalignment, Case 5 was measured with dual magnetic search coils in different gaze directions before and after surgery (3,4).

RESULTS

Figure 1 depicts the change in vertical and horizontal ocular misalignment of the 8 patients who were measured with the simultaneous prism and cover test at distance. Figure 1A shows the pre-OP and post-OP measurements, and Figure 1B depicts the post-OP and 1-year follow-up measurements. Preoperatively, 6 of the 8 patients presented with constant vertical misalignment. Two patients had intermittent diplopia with intermittent vertical misalignment (Case 4 and 8). Postoperatively, all patients were orthotropic and did not experience vertical diplopia. Stereopsis was present in all patients at the last examination (average stereopsis 275 sec-angle; range 200–600 sec-angle using the Lang stereopsis chart).

In 4 of the 8 patients, prism alternate cover testing showed vertical orthophoria at the post-OP visit at a viewing distance of 5 m. Four patients had residual hyperphoria of less than 5 prism-diopters (mean vertical misalignment from zero: 17.3 prism-diopters at pre-OP vs 0.75 prism-diopter...
The vertical phoria measured with the two-dimensional Hess screen test at a viewing distance of 0.3 m was also much improved (mean vertical misalignment from zero: 19.1° at pre-OP vs 3.94° at post-OP) (Fig. 1E). The alignment was stable at the 1-year follow-up visit (mean 1.69) (Fig. 1F), except for Case 5, initially the most undercorrected patient, who improved to nearly orthophoria. The reduction in vertical phoria between the preoperative and the 1-year follow-up visit was significant ($P = 0.0017$). Also, the horizontal phoria improved in the days after binocular vertical rectus muscle recession (mean misalignment from zero: 7.50° at pre-OP vs 4.75° at post-OP) (Fig. 1E) and between the postoperative and the 1-year follow-up visit (mean 3.25° at follow-up) (Fig. 1F). The reduction in horizontal phoria between the preoperative and the 1-year follow-up visit was also statistically significant ($P = 0.018$).

Figure 2 shows the Hess screen test of Case 5 preoperatively (Fig. 2A) and at the 1-year follow-up visit (Fig. 2B). The level of the thick black bar indicates the amount of left hyperdeviation and shows that this was comitant in left gaze, straight ahead (filled arrows), and right gaze. Also, the left hyperdeviation was comitant in the vertical gaze direction (empty arrows at 15° downgaze).

Figure 3A-C depicts the vertical misalignment in 15° left, straight ahead, and 15° right gaze for all 8 subjects and, as in Figure 3, is shown by the thick black horizontal bar at the preoperative visit (Fig. 3A), at post-OP (Fig. 3B), and at the 1-year follow-up visit (Fig. 3C). To determine whether vertical comitance changed after binocular vertical rectus muscle recession, regression lines between the gaze directions for each patient were fitted. The absolute values of the slopes of the regression lines did not vary much between the pre-OP and postoperative visit. There was also no large change between the postoperative measurement and the 1-year follow-up visit. Vertical misalignment was also measured in 15° upgaze, straight ahead, and 15° downgaze at the preoperative (Fig. 3D), post-OP (Fig. 3E), and the 1-year follow-up visit (Fig. 3F). Preoperatively, the incomitance was never greater than 5°. Directly after surgery, there was a transient incomitance present in 2 of the 8 patients that resolved without further intervention at the 1-year follow-up visit.

The field of single binocular vision of Case 5 is shown preoperatively in Figure 4A and at the 1-year follow-up visit (Fig. 4B). The area of fusion is enlarged for the entire study group after surgery (see median value in Fig. 4C, solid line). The size of the diplopia-free zone increased between the post-OP and the 1-year follow-up visit, with considerable variety among individual patients. This enlargement was not significant.

Fusion requires minimal horizontal, vertical, and torsional misalignment in each gaze direction. Using dual...
scleral search coils, all three components of eye direction within the 20° gaze field were simultaneously measured in Case 5. To clarify the torsional misalignment at different gaze directions, a three-dimensional Hess screen test (4) is presented. Fracture of the left orbital floor and orbital floor reconstruction 3 years before the strabismus surgery had caused this patient’s comitant vertical strabismus. Figure 5 depicts and numerically describes the misalignment of all three ocular rotation axes preoperatively (Fig. 5A, C) and 2 months after a 2.5-mm recession of the left superior rectus muscle and 2-mm recession of the right inferior rectus muscle (Fig. 5B, D). A slightly greater hyperphoria in right gaze compared with left gaze preoperatively (from left \[L/R\] 13.1° to \[L/R\] 17.1°, difference 4°) (Fig. 5C) was successfully diminished with slightly unequal (0.5 mm) recession of the vertical rectus muscles (from \[L/R\] 1.1° to \[L/R\] 2.5°, difference 1.4°) (Fig. 5D). Preoperative torsional misalignment was minimal. There was incyclo misalignment in left gaze and excyclo misalignment in right gaze. This pattern changed postoperatively to excyclotorsional misalignment in upgaze and incyclotorsional misalignment in downgaze.

**DISCUSSION**

The present study demonstrates that binocular vertical rectus muscle recession is effective in correcting comitant vertical strabismus in patients with normal retinal correspondence. Although introduced by Parks (5), this surgical option has not received attention (6). Recession of the superior rectus muscle in the hypertropic eye and recession of the inferior rectus muscle in the fellow
eye did not induce incomitance across the 15° vertical and horizontal field of gaze (Fig. 3) and consequently reestablished stereopsis. In addition, when fusion was active after binocular vertical rectus muscle recession (Fig. 1A-B), even horizontal phorias normalized significantly (Fig. 1C-F). With the reduction in misalignment after binocular vertical rectus muscle recession, the field of binocular fusion enlarged minimally after the operation and more so by the time of the 1-year follow-up visit (Fig. 4).

Binocular vertical rectus muscle recession is a straightforward approach to treating patients with comitant vertical strabismus. By performing equal or nearly equal recessions of the superior rectus muscle in the hypertropic eye and the inferior rectus muscle in the fellow eye, an overall and symmetrical improvement in alignment is achieved. Although we did not perform alternate and prism cover testing in convergent downgaze, patients did not report diplopia postoperatively in the reading position. The summation of both muscle recessions did not induce incomitance over a wide horizontal gaze range because one rectus muscle performs its vertical action most effectively in right gaze and the other in left gaze (5).

To reduce or eliminate vertical incomitant strabismus, a combined adjustable recession and posterior fixation suture of the same vertical rectus muscle is effective and therefore appropriate (7). In these patients, unilateral vertical rectus muscle recession with or without adjustable sutures can also be applied (8). However, when larger comitant vertical misalignment needs to be corrected a unilateral combined procedure such as recession of the superior rectus muscle and resection of the inferior rectus muscle in the hypertropic right eye would probably lead to a vertical overcorrection in right gaze and a vertical undercorrection in left gaze. Moreover, if only the superior rectus muscle in the hypertropic eye were recessed one would weaken not only its primary action as an elevator, but also its function as an incyclo rotator. That would cause excyclo rotation in the treated eye. If the inferior rectus muscle in the same eye were additionally resected an even larger excyclo rotation would result. Our patients’ misalignment showed balance in the torsional axis before and after the operation. This held true also in the two patients with fourth cranial nerve palsy as the initial cause of the misalignment. As stereovision was reestablished in our study patients, we may conclude that binocular vertical rectus muscle recessions symmetrically weaken the incyclo rotator in one eye and the excyclo rotator in the fellow eye. In Case 5, who was investigated with dual search coils, torsional misalignment of no more than 3° was measured. In this patient with an old orbital floor fracture this small amount of comitant torsional misalignment could be fused. However, if a larger torsional misalignment had been present, the surgeon may have considered an alternative approach.

In our series, neither ptosis nor lid retraction was induced perhaps because the recessions were small. This study does not claim that binocular vertical rectus muscle recession is superior to unilateral vertical muscle recession with or without the use of adjustable sutures. However, it does establish the efficacy of this surgical approach. Given that only 8 patients could be recruited in a 10-year period the incidence of comitant vertical strabismus in a single center is likely to be too small to allow comparison of different types of surgical treatment.

Acknowledgments

We thank the orthoptists at the Department of Ophthalmology, supervised by Brigitte Barlocher, who performed the pre- and postoperative measurements, as well as Hanna Obzina for recording the search coil.
measurements. We also thank Dominik Straumann and Michael C. Brodsky for their helpful comments on the manuscript.

REFERENCES
Ocular Misalignment in Graves Disease May Mimic That of Superior Oblique Palsy

Vicki M. Chen, MD and Linda R. Dagi, MD

Background: The Parks-Bielschowsky three-step test (TST) can incorrectly indicate that a superior oblique muscle is paretic in patients with restrictive strabismus. Although this pitfall in diagnosis has been widely reported, no large studies have examined the incidence of a positive TST in patients with Graves disease.

Methods: We performed a retrospective chart review of 31 consecutive patients with Graves orbitopathy examined at Children’s Hospital of Boston from 2003 to 2007. We analyzed ocular ductions, misalignment, and torsion, and thyroid function studies.

Results: Six (20%) of the patients had a positive TST, 3 (10%) of which showed excyclotorsion in at least one eye. However, of the 6 patients, 5 had obvious ocular adnexal signs of Graves disease and 2 had obvious supraduction deficits, leaving only 1 (3%) patient in whom the clinician would have mistakenly diagnosed a superior oblique palsy.

Conclusions: Although a positive TST occurs frequently in Graves disease, other clinical features should allow distinction from superior oblique palsy in most patients.


A positive Bielschowsky-Parks three-step test (TST) is traditionally interpreted as implicating a single paretic cyclovertical muscle (1), usually the superior oblique muscle. Traditional paradigms direct the surgeon to weaken the ipsilateral inferior oblique muscle or the contralateral inferior rectus muscle or to strengthen the ipsilateral superior oblique muscle (2).

However, restrictive myopathies, including Graves disease, can cause a restrictive TST and have been reported to mimic superior oblique palsy (3,4). In early Graves disease, findings of lid retraction or exophthalmos are not always clinically evident. If these soft tissue signs of Graves orbitopathy are subtle or absent, the finding of a positive TST may direct the surgeon to mistakenly diagnose a superior oblique palsy. Subsequent erroneous surgical treatments have the potential to cause disabling vertical and torsional diplopia. Although this pitfall in diagnosis has been widely reported, no large studies have examined the incidence of a positive TST in patients with Graves disease. To address this issue, we performed a retrospective study.

METHODS

The medical and ophthalmologic records of all patients with Graves disease evaluated in the senior author’s strabismus practice between 2003 and 2007 were reviewed. The diagnosis of Graves disease was based on clinical findings typical for hyperthyroidism and thyroid function studies, including elevated thyroxine (T₄), triiodothyronine (T₃), or free T₄, suppressed thyrotropin (TSH), positivity of TSH receptor antibodies (TBII), classic features of Graves orbitopathy, and confirmatory imaging documenting tendon-sparing enlargement of involved extraocular muscles.

Each patient was evaluated by prism and cover testing with fixation on a distant target. The misalignment of the eye was measured in prism-diopters (PD) in primary gaze, ipsilateral and contralateral side gaze, and ipsilateral and contralateral head tilt positions. Ductional excursions were noted in each patient. Excyclotorsion was measured using the double Maddox rod in a trial frame with the patient fixing on a light source located at a distance of 1 m. The patient was asked to adjust the Maddox rod orientation over each eye, and the degrees of torsion were recorded from the trial frame. The total torsion was calculated by adding the torsional measurements from each eye. Forced ductions were performed only on patients who underwent surgery.

An on-line PubMed literature review from 1935 to 2007 was performed using the following keywords: three-step test, Bielschowsky, Bielschowsky-Parks, and Graves disease.

Patients with known or suspected neurologic disease, cranial nerve palsies, or prior strabismus surgery were excluded from the study.
RESULTS
Thirty-one patients aged between 19 and 74 years were included. There were 19 women and 11 men.

Six (20%) patients had a positive TST, and 3 (10%) had excyclotorsion in at least one eye. Five of these 6 patients demonstrated ocular adnexal signs of mild Graves orbitopathy (2 with unilateral proptosis of 2 mm, 2 with lid retraction, and 1 with boggy edema of the lower eyelids bilaterally). The single patient (3% of the cohort) who had a positive TST and excyclotorsion without such adnexal signs had a preliminary diagnosis of a superior oblique palsy.

Of those patients with a positive TST, the average hypertropia (HT) was 7 PD in primary gaze, 17 PD on contralateral side gaze, and 12 PD on ipsilateral head tilt. Two of the 6 patients with a positive TST (33%) had a significant supraduction deficit of the hypotropic eye, strongly suggestive of restrictive strabismus. When torsion was present, the involved eye was always excyclotorted. The total torsion averaged 3 degrees. Three of the six patients with a positive TST (50%) demonstrated excyclotorsion that was greater in the hypertropic eye. Torsional misalignment in head tilt positions was not available for analysis.

DISCUSSION
Although the incidence of a positive TST was 20% in this study, the diagnosis of Graves disease was apparent in all but one patient (3%) on the basis of adnexal features of mild thyroid orbitopathy and clinical or biochemical manifestations of dysthyroidism. Our finding of excyclotropia in 50% of patients with Graves orbitopathy is in accord with that of Caygill (5), who found that 43% of patients had excyclotropia by the Maddox rod test, and that of Trobe (6), who found that 8 (55%) of 15 patients had excyclotorsion greater than 5.

Bielschowsky (4) and Kushner (3) have highlighted the possibility of error in the diagnosis of superior oblique palsy. Kushner (3) reported 7 patients with a positive TST who did not have a superior oblique palsy, only one of which had Graves orbitopathy. Metz (7) also reported that restrictive orbitopathy may mimic cranial nerve palsies but did not document whether Graves disease was one of those restrictive entities.

FIG. 1. Proposed mechanism for a positive TST in Graves disease with restricted left inferior rectus muscle. A. Schematic version, left eye fixing. Right hypertropia is present in primary gaze due to a restrictive left inferior rectus muscle. The right hypertropia increases in contralateral side gaze because of the increased tone of the left inferior rectus muscle in left gaze. On ipsilateral head tilt, the increased tone of the left inferior rectus results in substantial infraduction, thereby increasing the right hypertropia and also causing excyclotorsion. B. Clinical version, left eye fixing. There is a right hypertropia due to a restrictive left inferior rectus muscle. C. Schematic version, right eye fixing. There is a right hypertropia in primary gaze due to a restrictive left inferior rectus muscle. The right hypertropia increases in contralateral side gaze because of the increased tone of the left inferior rectus muscle in left gaze. On ipsilateral head tilt, the increased tone of the left inferior rectus results in substantial infraduction, thereby increasing the right hypertropia and also causing excyclotorsion. D. Clinical version, right eye fixing. There is a right hypertropia due to a restrictive left inferior rectus muscle.
Moster et al (8) described 6 patients with a positive TST in whom hyperthyroidism was eventually diagnosed. The mechanism by which Graves disease caused a positive TST was not discussed.

We propose a mechanism based on recent physiologic force-tension studies (9,10) in patients with Graves disease. The steady-state tension ($F_s$) was significantly higher in patients with more advanced Graves disease than in patients with milder disease. We propose that a positive TST occurs because of increased tension in the involved muscle (Fig. 1). The inferior rectus muscle is the most common vertical rectus muscle affected in Graves orbitopathy. The unilateral infiltration of one inferior rectus or the asymmetric involvement of both inferior recti would result in the following pattern of deviation. The increased tone of the more active inferior rectus in one eye may cause a contralateral hypertropia. On gaze contralateral to the hypertropic eye, the hypotropic eye is placed in abduction, and the inferior rectus is in a position to exert maximal force of contraction, resulting in greater vertical misalignment than is seen on gaze contralateral to the hypertropic eye. On gaze ipsilateral to the hypertropic eye, the hypotropic eye is placed in adduction, and the inferior rectus is only weakly activated, resulting in less vertical misalignment than is seen on gaze contralateral to the hypertropic eye. On head tilt ipsilateral to the hypertropic eye, excyclotorsion is stimulated in the hypotropic eye, and the inferior rectus, with greater tone, increases the observed vertical misalignment. On head tilt contralateral to the hypertropic eye, intorsion is stimulated in the hypotropic eye, which does not activate the inferior rectus muscle of the hypotropic eye. The vertical misalignment would therefore appear greater on head tilt ipsilateral to the hypertropic eye than on head tilt contralateral to the hypertropic eye. Figure 1A, C illustrates the mechanism of a positive TST in patients with Graves orbitopathy. The diagrams are shown with left and right eye fixing, respectively, to demonstrate the variation in clinical presentation. Illustrative clinical photos are shown in Figure 1B, D.

As unilateral or bilateral and asymmetric inferior rectus enlargement is a common finding in Graves orbitopathy and a frequent occurrence in the setting of vertical misalignment with this disorder, our model suggests that a predictably high percentage of patients with vertical misalignment in this condition will have a positive TST.

The most common surgical treatment for superior oblique palsy is ipsilateral inferior oblique weakening. This procedure would not typically be the surgical approach chosen to remedy vertical misalignment due to Graves orbitopathy and might exacerbate vertical and torsional misalignment. Orbital imaging, clearly helpful in diagnosing early Graves orbitopathy, may not be considered in cases of presumed isolated superior oblique palsy. Its absence might delay the correct diagnosis.

REFERENCES
ORIGINAL CONTRIBUTION

Impairment of Vertical Saccades From an Acute Pontine Lesion in Multiple Sclerosis

Alessandra Rufa, MD, PhD, Alfonso Cerese, MD, Lorenzo De Santi, MD, Marco Mandala’, MD, Daniele Nuti, MD, Antonio Giorgio, MD, and Pasquale Annunziata, MD

Abstract: A 62-year-old woman with relapsing-remitting multiple sclerosis suddenly complained of diplopia associated with bilateral adduction impairment, nystagmus of the abducting eye bilaterally, and sparing of abduction, convergence, and vertical eye movements, consistent with bilateral internuclear ophthalmoplegia. Within 1 week, she had developed a complete horizontal gaze paralysis even with the oculocephalic maneuver. Vertical saccades were slow and convergence was preserved. There was a right lower motor neuron seventh cranial nerve palsy. Brain MRI showed a new enhancing lesion involving the pontine tegmentum. Clinical and MRI follow-up showed recovery after 6 months. The slowing of vertical saccades may have been due to spread of the demyelinating lesion to the adjacent paramedian pontine reticular formation, which contains omnipause neurons lying in the raphe interpositus nucleus thought to inhibit excitatory burst neurons for horizontal and vertical saccades. Our patient verifies the fact that vertical saccadic abnormalities may occur from a lesion apparently confined to the pons.


Nearly 30% of patients with multiple sclerosis (MS) experience internuclear ophthalmoplegia (INO) at some time during the course of disease (1). This eye movement disorder is caused by a lesion of the medial longitudinal fasciculus (MLF). In some patients, adjacent structures may be involved, causing a more complex clinical picture, including complete horizontal gaze paralysis (2). Recently, unusual ocular motor findings have been described in patients with MS, including bilateral third nerve palsy, opsoclonus, and isolated sixth cranial nerve palsy (3). Here, we report the case of a patient with MS who presented with acute bilateral INO followed 1 week later by complete transient horizontal gaze paralysis associated with slow vertical saccades. This patient verifies the fact that a lesion apparently confined, by imaging criteria, to the pons can cause a vertical saccadic impairment.

CASE REPORT

A 62-year-old woman with relapsing-remitting MS diagnosed at age 44 complained of diplopia for 4 days. She denied previous episodes of diplopia and previous examinations had revealed no ocular motor abnormalities. She was not undergoing immunomodulatory or immunosuppressive treatment.

Neurologic examination showed complete adduction loss and nystagmus of the abducting eye bilaterally. Abduction, convergence, and vertical eye movements were spared. A diagnosis of bilateral INO was made. Examination 48 hours later showed complete horizontal gaze paralysis even with the oculocephalic maneuver. The vertical vestibular-ocular reflex (VOR) was clinically normal, but vertical pursuit was interrupted by saccades. Vertical saccades appeared slow, but convergence was preserved. There was also a right lower motor neuron seventh cranial nerve palsy.

Treatment with intravenous methylprednisolone (1000 mg/day for 5 days) was started and, after a few days, adduction dramatically improved in both eyes, followed by gradual restoration of vertical eye movements.

Brain MRI, performed 21 days after the onset of complete horizontal gaze paralysis, showed a T2 lesion located at the right pontine tegmentum with extension to the left side. This lesion had not been present on an MRI performed 7 months earlier. Only the right side of the lesion enhanced on T1. No enhancing lesions were observed in the midbrain or elsewhere in the brain (Fig. 1).
Two months later, vertical movements, bilateral adduction, and the right lower motor neuron seventh cranial nerve palsy had recovered completely, whereas abduction lag persisted and transient horizontal diplopia was reported. Six months later, there was complete recovery of ocular movement. MRI showed that the brainstem lesion had disappeared.

DISCUSSION
Complete unilateral or bilateral horizontal gaze paralysis implies lesions of the pontine tegmentum involving the sixth cranial nerve nucleus with or without involvement of the paramedian pontine reticular formation (PPRF) (4). Although seldom reported in MS, unilateral lesions of the sixth cranial nerve nucleus are usually associated with damage to the seventh cranial nerve fascicle and may involve other adjacent structures controlling horizontal and vertical eye movements, such as the MLF or PPRF (2,4). In our patient, bilateral INO occurred first, followed 1 week later by involvement of the right sixth cranial nerve nucleus and left sixth cranial nerve fascicle. This resulted in complete horizontal gaze paralysis.

We hypothesized a lesion involving the sixth cranial nerve nucleus and its fascicles on the right side, but restricted to the sixth cranial nerve fascicles on the left side, as function of the left seventh cranial nerve fascicles, which travel next to the sixth cranial nerve nucleus, was spared. There is a previous report (5) of two subjects with MS who had bilateral INO at onset, followed a few days later by bilateral loss of abduction resulting in complete horizontal gaze paralysis. The authors suggested that the demyelinating lesion first involved both MLFs and spread centrifugally to affect the sixth cranial nerve motor fibers on both sides. In those 2 patients, however, vertical saccades were reported to be normal.

In our patient, we hypothesized lesion progression as shown in Fig. 2. Bilateral INO is often associated with impairment of vertical pursuit and VOR, as MLFs convey ascending signals for vertical vestibular reflexes, smooth pursuit, and gaze holding from the vestibular nuclei to the third and fourth cranial nerve nuclei and the interstitial nucleus of Cajal (6). Vertical saccades are not impaired by lesions of the MLFs. In our patient, the slowing of vertical saccades may have been due to spread of the demyelinating lesion to the adjacent PPRF. The PPRF consists of three subgroups of neurons from rostral to caudal: excitatory burst neurons (EBNs) lying in the medial part of the nucleus reticularis pontis caudalis (NRPC), omnipause neurons (OPNs) lying in the raphe interpositus nucleus (RIP), and inhibitory burst neurons (IBNs) lying in the nucleus paragigantocellularis dorsalis (PGD) (7). The slowing of vertical saccades could have been due to a lesion of RIP involving OPNs. In fact, OPNs have been shown to induce a prevalent glycnergic inhibition of EBNs in the pons and midbrain during fixation (8).

Indeed, EBNs in the PPRF discharge only weakly for vertical saccades (9), whereas damage confined to OPNs causes slowing of horizontal and vertical saccades (10). As previously observed by Milea et al (5), we also suggest that in our patient, the course of ocular abnormalities was due to medial-lateral progression of the brainstem lesion. However, in our patient, lesion extension was more evident on the right where the seventh cranial nerve fascicle was affected, causing a right seventh cranial nerve palsy. The MLFs, which were involved at onset, were the first to recover. Subsequent centrifugal spreading transiently involved OPNs in the RIP, and then the adjacent sixth cranial nerve fascicles,
which recovered more slowly, as suggested by persistence of the abduction lag 2 months later. Extension of the demyelinating lesion toward the rostral interstitial nucleus of the MLF (riMLF), which takes part in the generation of fast vertical eye movements, should also be considered as a possible explanation for the impaired vertical saccades. In humans, the riMLF nucleus lies just above the nucleus of Cajal and third cranial nerve nucleus and dorsomedially to the anterior pole of the red nucleus (11). However, the more recent lesion of this patient was in the pontine tegmentum and did not involve the midbrain. Furthermore, vertical eye movement limitations, convergence impairment, or diplopia had not been demonstrated earlier.

Our report suggests that demyelinating lesions confined to the pons may lead to impairment of vertical saccadic eye movements.

REFERENCES

Perimetry While Moving the Eyes: Implications for the Variability of Visual Field Defects

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Background: In standard perimetry, subjects fixate so that saccades are reduced and testing precision is increased. However, because vision in daily life requires eye movements, it is appropriate to assess visual fields during eye movement.

Methods: Perimetry was carried out in 8 healthy subjects and in 16 patients with visual field defects under conditions of a stable and moving fixation spot. Eye movements were simultaneously recorded with an eye tracker. Outcome measures included stimulus detection, variability of visual field border, and saccade amplitudes.

Results: Perimetric performance during stable fixation was comparable to that during eye movement. All subjects showed 92%–96% correct detections of the fixation controls and a stable and comparable blind spot position in the stable and moving fixation spot conditions. The eye tracker revealed that 97% of the time the eyes were positioned within 61 from fixation.

Conclusions: Visual fields obtained by perimetry while moving the eyes is comparable to standard perimetry in which a stable fixation spot minimizes eye movements.


Perimetric results are prone to eye movement artifacts (1,2). In standard perimetry, patients are asked to continuously look at a fixation spot test to reduce the influence of saccadic eye movements. Conventional perimeters typically include methods to control fixation errors. Despite such measures to control eye movements, visual fields are somewhat unstable, with test-retest variability of approximately 62 of visual angle on conventional and computer-based perimetry (3,4).

In real-life situations, such as during locomotion or driving a vehicle, it is necessary to scan the surrounding environment with eye movements to avoid collisions and accidents (5-7). Standard perimetry may therefore be considered somewhat artificial. In fact, patients often complain about blurred vision, double images, and hallucinations, which may result from a lack of eye movements. These side effects of constant fixation may be explained in part by Troxler’s fading effect (8). Troxler noticed in 1804 that when one fixates a particular point, a stimulus presented in the peripheral visual field will gradually fade away and disappear after about 20 seconds. The effect is enhanced if the stimulus is small and of low contrast (8). Spillmann et al (8) found that even moving targets will rapidly fade quickly in the field periphery. It is a well-known principle in perception that unvarying stimuli soon disappear from awareness. To avoid this effect, the eyes must constantly move. If they were perfectly motionless, photoreceptors would not be sufficiently stimulated and visual perception would “bleach.” Holding the eye position constant during fixation for up to 20 minutes at a time creates discomfort and inattention which could, in turn, produce spurious results (9).

To eliminate the need for continuous fixation, oculokinetic perimetry, in which the patient moves the eyes around a central static target to look sequentially at an array of numbers, was developed (10) as a method of visual field assessment. When fixation on a number is accompanied by disappearance of the central target, that number is deleted from a recording chart. Inversion of the recording chart gives a plot of the central visual field (11,12).

Because the precise measurement of visual fields is critical to determine the size of the deficit and possible recovery of visual function, we have created a perimetric task that uses a moving fixation spot that might be more natural. This moving fixation spot was intended to simulate a more physiological situation by inducing smooth pursuit eye movements and thereby reduce the influence of random eye movements during perimetry.

Our experiment follows those of other investigators. A moving fixation spot perimeter, computer-assisted moving eye perimeter (CAMEC), was described by
Johnston et al (13), whereby the patient looks at a moving fixation target on a high-resolution monitor and tries to keep it inside a circle using a joystick. This test was developed for children to increase their motivation during perimetry. However, this method requires continuous eye movement, which increases the retinal area each stimulus can excite. It also binds attention to the fixation spot, which leads to decreased attention for peripheral target stimuli. Consequently, the position of the blind spot was found at rather variable distances from the fovea (14). Mutlukan and Damato (15) investigated children with the blind-spot program of the CAMEC and the Dicon Auto-Perimeter, which has a moving fixation spot. The blind spot was detected in 75% of the 32 children by the Dicon Auto-Perimeter and in 100% by CAMEC. CAMEC allowed better detection and quantification of scotomas in patients older than 4 years. Mutlukan et al (16,17) investigated the position of the blind spot and detection of glaucomatous visual field loss with a multi-fixation campimeter. This device has a central test stimulus and a series of numbered fixation targets and uses the patient’s eye movements to position the stimulus in the visual field. Haarmeier and Thier (18) compared a stationary and a moving fixation spot to test whether smooth pursuit eye movements improve the detection of speed changes.

To avoid problems such as the Troxler phenomenon, we have developed a computer program for perimetry with an oscillating fixation spot. We hypothesized that this moving spot would 1) reduce saccades into the periphery, 2) improve stability of fixation, 3) increase precision of perimetry, and 4) improve comfort. Because nothing is known about the optimal amplitude and frequency of oscillation of this moving fixation spot, we first carried out a pilot study to address this issue. We then compared visual fields under stationary and moving fixation spot conditions.

METHODS

Participants

We recruited 8 healthy subjects (5 men and 3 women, mean SD age 42 ± 12.2 years) and 16 patients with visual field defects (11 men and 5 women, age 55 ± 17 years) through newspaper advertisements (Table 1). Visual field defects were due to glaucoma (n = 2), cerebral bleeding (n = 1), retrochiasmal ischemic stroke (n = 6), surgery for brain tumor (n = 1) and epilepsy (n = 1), retinal detachment (n = 1), optic neuritis (n = 1), multiple sclerosis (n = 2), and central retinal artery occlusion (n = 1). Figure 1 displays the visual fields obtained with high-resolution perimetry (HRP) for all study participants. Because the aim of our study was to compare performance under different perimetric testing conditions and not to describe a particular patient sample, we believed that a more homogeneous patient population might have been more adequate, but it would have reduced our ability to generalize our findings to a heterogeneous patient population as typically seen in clinical practice. Furthermore, for the determination of reaction time and fluctuation of visual field defects, the underlying cause of the deficit did not matter.

The control subjects and the patients were comparable with respect to age. Inclusion criteria for the control subjects were no detectable visual field defects and no known neurological or ophthalmological illnesses. The inclusion criterion for the patients was the documentation of a visual field defect by at least one perimetric evaluation before study entry. Exclusion criteria for all participants were age < 18 years, visual acuity < 0.15, hemispatial neglect, severe cognitive deficits making them unable to comply with instructions, photosensitive epilepsy, psychosis, attention deficits, impairments in motor performance, and a history of having undergone more than five perimetry tests during the last 12 months.

Perimetric Procedure

Suprathreshold HRP tests were carried out monocularly with the eyes at a 30-cm distance from a 17-inch computer monitor. A grid of 475 points within ± 27 horizontally and ± 22 vertically was tested. The stimulus size was 0.15° with 76 cd/m² luminescence and 38 cd/m² background luminescence (19). We compared perimetric performance under stationary and moving fixation spot conditions. For the stationary condition, we carried out three repeated tests. For the moving fixation spot condition, we carried out two repeated tests with a slower speed (2°/s) and two repeated tests with a faster moving fixation spot (speed 3°/s). Each perimetry session lasted about 20 minutes. To reduce head movement artifacts, the head was fixated on a chin-forehead rest. During the test, horizontal eye movements were measured by an infrared eye tracker with high temporal and spatial resolution (Chronos Vision Eye Tracker, measuring 200 frames/s with accuracy of approximately ± 0.1°).

We have used the stationary fixation spot in our studies previously (19-23). It has a visual angle of 0.14. The fixation control consists of a color change detection task. At random intervals, the fixation spot changes its color from light green to light yellow. The subject must fixate continuously and respond to these color changes by pressing a key on the computer key board each time the color change is detected. The number of correct detections of such color changes is used as a measure of fixation ability. In contrast, the moving fixation spot swings horizontally ± 1° in each direction at a speed of 2 or 3/s. Subjects were instructed to follow this spot with eye movements while holding the head steady. At the inflection point, the fixation spot took a 200 ms “break” (stationary


### TABLE 1. Demographic and etiologic data of study sample

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Tested Eye</th>
<th>Acuity Right Eye</th>
<th>Acuity Left Eye</th>
<th>Lesion Side</th>
<th>Lesion Location</th>
<th>Etiology</th>
</tr>
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<tbody>
<tr>
<td>C1</td>
<td>M</td>
<td>45</td>
<td>R</td>
<td>0.9</td>
<td>0.8</td>
<td>—</td>
<td>—</td>
<td>Normal</td>
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<td>M</td>
<td>64</td>
<td>R</td>
<td>0.8</td>
<td>0.8</td>
<td>—</td>
<td>—</td>
<td>Normal</td>
</tr>
<tr>
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<td>M</td>
<td>44</td>
<td>L</td>
<td>1.40</td>
<td>1.40</td>
<td>—</td>
<td>—</td>
<td>Normal</td>
</tr>
<tr>
<td>C4</td>
<td>F</td>
<td>29</td>
<td>L</td>
<td>1.24</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
<td>Normal</td>
</tr>
<tr>
<td>C5</td>
<td>F</td>
<td>45</td>
<td>L</td>
<td>0.63</td>
<td>0.80</td>
<td>—</td>
<td>—</td>
<td>Normal</td>
</tr>
<tr>
<td>C6</td>
<td>F</td>
<td>23</td>
<td>L</td>
<td>1.00</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
<td>Normal</td>
</tr>
<tr>
<td>C7</td>
<td>M</td>
<td>43</td>
<td>L</td>
<td>0.7</td>
<td>0.8</td>
<td>—</td>
<td>—</td>
<td>Normal</td>
</tr>
<tr>
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<td>M</td>
<td>44</td>
<td>L</td>
<td>1.25</td>
<td>1.25</td>
<td>—</td>
<td>—</td>
<td>Normal</td>
</tr>
<tr>
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<td>R</td>
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<td>Surgery due to brain tumor</td>
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<tr>
<td>P2</td>
<td>F</td>
<td>54</td>
<td>R</td>
<td>0.8</td>
<td>0.8</td>
<td>B</td>
<td>Optic nerve</td>
<td>Multiple sclerosis</td>
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<td>42</td>
<td>L</td>
<td>0.20</td>
<td>0.50</td>
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<td>Retina</td>
<td>Glaucoma</td>
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<tr>
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<td>L</td>
<td>0.60</td>
<td>0.16</td>
<td>L</td>
<td>Retina</td>
<td>Glaucoma</td>
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<td>L</td>
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<td>0.80</td>
<td>R</td>
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<td>Hippocampectomy right (surgery for epilepsy)</td>
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<td>R</td>
<td>Retina</td>
<td>Right retinal thrombosis</td>
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<td>0.80</td>
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<td>Cortical</td>
<td>Ischemic infarct</td>
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<td>F</td>
<td>68</td>
<td>R</td>
<td>1.00</td>
<td>1.00</td>
<td>B</td>
<td>Optic radiation and cortical</td>
<td>Ischemic infarct</td>
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<td>R</td>
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<td>R</td>
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<td>Multiple sclerosis</td>
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<td>0.50</td>
<td>R</td>
<td>Retinal</td>
<td>Right retinal ablation</td>
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<td>L</td>
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<td>0.80</td>
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<td>Cortical</td>
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<td>R</td>
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<td>0.60</td>
<td>R</td>
<td>Optic radiation and cortical</td>
<td>Ischemic infarct</td>
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<tr>
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<td>M</td>
<td>63</td>
<td>L</td>
<td>0.80</td>
<td>1.00</td>
<td>R</td>
<td>Cortical</td>
<td>Ischemic infarct</td>
</tr>
</tbody>
</table>

F, female; M, male; L, left; R, right; B, both sides of the visual field.

Position (and a perimetric target stimulus was presented for 150 ms elsewhere on the screen at one of 475 positions. To control for possible false alarms, the stimulus was given only in 80% of all inflexions.

To validate the results of the suprathreshold HRP with conventional near-threshold perimetry, we also carried out 3 examinations on the Tuebinger Automated Perimeter 2000 (24). Here the stimulus size was 0.14° and the intensity varied stepwise between an individual threshold level and 1000 cd/m². The inner 30 of the visual field were tested with a 90-point test grid. Background light was 10 cd/m². Each target point detected at a luminescence of 100 cd/m² or below was defined as being "intact." Between perimetric sessions, participants were allowed a break of at least 15 minutes. No more than four tests were carried out on a given day. After each test, a questionnaire was used to assess the level of discomfort (exertion) and possible side effects during the test. Each patient had to carry out all perimetric tests within a maximum period of 2 weeks.

We decided against the use of a refractive error correction because contact lenses or spectacles would have interfered with the proper function of an eye tracker (see below), which uses cornea reflections to measure eye position. This step is permissible because, although the detection threshold is elevated when the refractive error is not corrected, neither the localization of the visual field defect nor the variability of perimetric performance is altered.

**Eye Movement Recordings**

During HRP eye movements were recorded with a Chronos Vision Eye Tracker (23). Before each
examination, this system was individually calibrated using a fixation spot and 4 points at a distance of 10s from the center. The coordinates of the eye position were obtained by detecting the center of the pupil 200 times/s. With use of this technology, smooth pursuit eye movements created by the subjects as they followed the uniform motion of the horizontally swinging fixation spot could be visualized as a regular sinus curve in the x-axis eye tracker data (Fig. 2).

In contrast, saccades leaving the path of the swinging fixation spot were seen as clearly visible spikes away from the sinus-like baseline curve. By quantifying such spikes, we were able to differentiate between smooth pursuit eye movements and aberrant saccadic eye movements. The
FIG. 2. Smooth pursuit eye movements following the moving fixation spot of the horizontal x-axis measured by an eye tracker. The point is swinging at an amplitude of 2° (=2 boxes in ordinate); 1 box in abscissa = 2.5 seconds.

number of such aberrant saccadic drifts was counted as an indicator of fixation instability. To be counted as a deviation from the sinus-like baseline curve, the following criteria (25-34) applied:

- Saccadic duration between 15 and 1000 ms;
- Saccadic velocity of at least 15°/s up to 750°/s;
- Deviation from the (moving or stationary) fixation spot for at least 100 ms.

We classified all saccadic eye movements within these limits as aberrant drifts. Movements that did not qualify for this definition were defined as head or body movements or other artifacts and were ignored. The analysis of eye tracker raw data was done by TETGaze-count, a program developed in our laboratory by one of the authors (TG).

Outcome Measures

One goal of our experiment was to show the degree to which visual field variability in perimetry is influenced by eye movements. Therefore we analyzed the variability of the visual field border between the intact and the defective area by measuring the horizontal distance from the 0-vertical meridian at positions 0°, 5°, 10°, 15°, and 20° of visual angle above and below the visual field center (Fig. 3). In patients with unilateral visual field defects, these measurements refer to the defective half-field only. In patients with visual field defects in both hemifields, we calculated the mean distance between the vertical meridian and the left and right visual field borders. Many patients had no clear border between the intact and the defective visual fields but a large transition zone and scattered relative defects. Because single “blind” positions in an otherwise intact field may be artifacts due to blinking, we

FIG. 3. Results of high-resolution perimetry. Black squares indicate areas of the visual field in which the subject did not respond to stimulus presentation. White indicates response in the predetermined time window. The arrows show how the visual field borderline was determined at 9 different positions. This example was taken from the left eye from a patient with a left homonymous hemianopia. The blind spot was only measured in healthy subjects (circle, fixation spot; black, blind; white, intact visual areas). The x- and y-axes show degrees of visual angle.
devised the following definitions of a visual field border. We measured the distance between the vertical meridian and the first stimulus location with a minimum of two undetected stimuli in a row. The standard error of the variability of the visual field borders between different tests was taken as an indicator of test reliability. In healthy subjects without defective visual field areas, the $x$-coordinate of the blind spot was measured and its fluctuation was compared between the tests.

**Subjective Reports**
In our past studies, patients frequently reported side effects of visual field testing. Therefore we developed a 7-item questionnaire to assess the following side effects of testing:
- Tears in eyes during the perimetry
- Burning of eyes during testing
- Double images of the central fixation spot
- Blurring of the fixation spot
- Visual hallucinations
- Foggy images
- Illusion of a bright frame around the test field

Subjects had to rate each side effect on a scale from 0 (never occurring) to 5 (occurring frequently). In addition, we asked the subjects to rate their overall exertion after every separate perimetric investigation. The participants did not know which test method was the newly developed one (single-masked condition).

**Statistical Analysis**
Variability of visual field borders in patients and positions of the blind spot coordinates in subjects were measured by calculating the mean variances of these coordinates for each subject during each of the following three conditions: perimetry with stable fixation, with a slower moving fixation spot, or with a faster moving fixation spot. We used analysis of variance (ANOVA) for repeated measurements to compare the variability between the three test conditions. Pair-wise post hoc comparisons between conditions were done using Bonferroni adjustments. To analyze the correlation between eye movements and visual field variability, we classified the saccadic drifts as small (1-2°) or large (>2°) and calculated the Pearson’s rank correlation coefficient with measures of visual field variability (standard errors of measurement).

All subjects were assigned in stratified groups which determined the order in which the tests were carried out. Randomization was done by computer-generated group assignments. Possible differences in comfort during testing and intensity of side effects among the different perimetric procedures were checked by using ANOVA for repeated measurements.
FIG. 4. Intertest variability (expressed as standard error) of the visual fields in patients and control subjects under different perimetric conditions: stable fixation point, slower or faster moving fixation point on a computer-based high resolution perimetry and when assessed by Tuebinger automated perimetry. Left. Average variability of the blind spot x-axis in healthy subjects. Right. Average variability of the visual field borderline (x-axis) in patients as determined by the method shown in Fig. 2. The y-axis displays the variability (standard error of the mean) in degrees of visual angle. The figure shows that the variability is greater in patients that in healthy control subjects.

Reliability of Different Perimetric Methods in the Blind Spot Measurements

In control subjects, only the blind spot could be used as a measure of variability of visual field investigations. In the stable fixation spot condition, the average position of the blind spot in healthy subjects was 16.35 ± 0.55° from the midline at the x-coordinate and 1.73 ± 1.36° at the y-coordinate. This value did not differ significantly from the other methods using the slower (x 16.69 ± 0.60° and y 1.83 ± 1.68°) or faster moving fixation spot (x 16.51 ± 0.78° and y 1.85 ± 1.58°) and TAP (x 16.11 ± 0.88° and y 1.74 ± 1.63°).

Correlation Between Variability of Blind Spot Measurements and Eye Movements

The correlation between the variability of the blind spot coordinates and saccadic eye movements was small and negative (stable fixation spot: r = 0.434, NS) (Table 3).

<table>
<thead>
<tr>
<th>Test</th>
<th>Correlation Between Visual Field Fluctuations and Total Eye Movements</th>
<th>Correlation Between Visual Field Fluctuations and Eye Movements &gt;2 degrees</th>
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<tr>
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<td>Spearman Rho</td>
<td>P &lt;</td>
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<tr>
<td>Stable fixation spot</td>
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<tr>
<td>Slower moving fixation spot</td>
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</tr>
<tr>
<td>Faster moving fixation spot</td>
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<td>0.534</td>
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</table>
This result shows that a higher variability of the blind spot position was not related to the number of saccadic eye movements.

Subjective Comfort During Tests and Side Effects
The trials with a moving fixation spot did not lead to less exertion. Exertion showed values of 1.92 ± 1.41 with the slower moving fixation spot and 2.12 ± 1.24 with the faster moving fixation spot in the control subject group. Exertion values in the visual impaired group were between 1.86 ± 0.87 (slower moving fixation spot) and 2.36 ± 1.23 (faster moving fixation spot). There were no significant differences between the tests with stable and with a moving fixation spots (Wilks lambda multivariate test l = 0.809, P = 0.226). The control subject and patient groups did not differ (Fig. 5).

Side Effects
Side effects did not differ significantly between the three perimetric methods. The average score for all seven items was between 3.3 ± 3.4 (faster moving fixation spot) and 4.5 ± 5.0 (stable fixation spot). The slower moving fixation spot had an item score of 4.7 ± 5.2. TAP had a 3.7 ± 3.1 item score. There was no significant advantage for the moving fixation spot in any of the items. Thus, the moving fixation spot produced as much exertion during perimetry and the side effects could not be reduced by this new fixation method (Fig. 6).

DISCUSSION
The main goal of our experiment was to determine whether visual fields obtained by perimetry with and without eye movements differed from each other. Another goal of the study was to evaluate whether computer-based perimetry with a moving fixation spot might be more convenient for patients and reduce possible influences of continuous fixation of a stationary spot as used during standard perimetry.

Moving fixation spot perimetry was found not to be more comfortable for control subjects or patients than perimetry where the eyes have to be suppressed by fixating a stable fixation point. There were no significant differences either in the assessment of comfort or in the reduction of uncomfortable side effects. Our finding is not in agreement with that of Wong et al (35), who noted that use of the Humphrey Field Analyzer and the Dicon TKS 4000, with a moving fixation target during Dicon testing, makes visual field testing more comfortable for patients. Asman et al (36) also evaluated the fixation accuracy of static (Humphrey Field Analyzer) and kinetic fixation (Dicon) perimetry and determined their ability to detect the absolute scotoma of the physiologic blind spot. In patients with glaucoma, the frequency of fixation errors was significantly greater for kinetic (17.2%) than for static (10.2%) methods. The authors concluded that kinetic perimetry was associated with greater fixation inaccuracy and underestimation of the absolute scotoma at the physiologic blind spot.

Our method of presenting target stimuli at the inflection points of the moving fixation spot led to visual detection that was comparable to perimetry with a stable fixation point. This result implies that introducing eye movements has little or no effect on perimetric performance. This result also contrasts with prior observations by Demirel (4), who found a significant influence of eye movements on perimetry results but only if the eye positions exceeded ±1° amplitude more than 20% of the time. Also, in patients with glaucoma, Henson et al (37,38) found that fixation was within 0.5° of the target in only 7% of the presentations, whereas it was at best within this range in about 60% of presentations.

By contrast, in our study we found that fixation was within an area of ±1° about 97% of the time (during only 3% of the testing time were saccades larger than 1°). This result is similar to that of Kasten et al (23), who found eye positions ±1° away from a stable fixation spot in 81.6% and up to 2 away in 94.8% of the overall testing time. We clearly found that saccades have smaller effects on perimetric performance than other studies have suggested.
FIG. 5. Results of the exertion question. Test conditions were the same as in the legend to Figure 4. Exertion was rated by the subjects on a scale from 0 (easy) to 5 (very hard). The bars display the different fixation point conditions for the control subjects and patients combined: stable fixation spot, slower and faster moving fixation spot, and exertion for the standard perimeter.

In previous investigations (20), variability of the visual border position was $\pm 2.2^\circ$ in perimetric tests repeated five times in each patient. In our study, the SEM was $\pm 2.6^\circ$ in three independent measurements. A significant positive correlation between eye movements and this SEM of visual field borders was found only within tests using a stable fixation spot. Tests with the moving fixation spot did not show any significant influence of eye movements on visual field fluctuation. We conclude that eye movements only slightly influence perimetric results.

To be able to estimate the variability of visual field testing under the different perimetry conditions, we assessed the variability of the blind spot position in the control subjects. It was between $\pm 0.42^\circ$ and $\pm 1.04^\circ$, less than half of what we found in the group of patients with a variety of visual field defects. In control subjects, the blind spot variability and in patients the variability of visual field defects was relatively independent of eye movements because we did not find a positive correlation between eye movements and visual field fluctuations. Apart from eye movements, then, there are other influences such as attentional fluctuations (39,40) that contribute to the fluctuation of visual field border positions in patients. Another influence may be the existence of “areas of residual vision” (also termed “relative defects” or “transition zones”), which are typically located between the visual field defect and the intact visual field. In these areas, stimuli are seen unreliably, perhaps as a functional expression of residual visual structures in the damaged brain (21). The existence of areas of residual vision in patients might also be corroborated by the fact that variation of the blind spot in healthy persons is significantly lower ($0.77^\circ$) than variation
of the visual field border positions (2.6°). Based on these values, we estimate that only up to one fourth of the variability of visual field border is caused by eye movements.

Several additional factors contribute to visual field variability in normal subjects and in patients with optic neuritis, glaucoma, or ocular hypertension. Henson et al (38) found decreased brightness sensitivity, whereas stimulus eccentricity, patient age, fixation loss rate, and false-positive rate did not predict response variability.

In our study, a higher variability of the position of the center of the blind spot was not related with an increasing number of saccadic eye movements. This result could be explained by the fact that saccades exceeding 2° of visual angle occurred only 1% of the time. Visual field fluctuations were significantly correlated with eye movements in the stable fixation condition ($R = 0.645$), whereas there were no significant correlations in the conditions with the moving fixation spots. Therefore, it remains unclear whether patients with large areas of residual vision make more saccadic eye movements and if they are directed toward or away from the hemianopic field. This issue requires additional research.

It has been argued that patients with visual field defects compensate for their deficit by making more frequent eye movements toward the hemianopic field and that visual field enlargements found after vision restoration therapy (VRT) may be an artifact of such eye movements (41). On the other hand, Henson et al (37,38) concluded that fixation errors, although contributing to variability, are not the major cause of the increased variability seen at locations with reduced sensitivity. In our study, patients with visual field defects did not show more eye movements than visually healthy subjects. Large saccades were very rare. This result argues against the proposal that areas of residual vision ("relative defects") or their enlargement are exclusively an artifact of eye movements (41,42). Even so, when studies on recovery and restoration of visual field

FIG. 6. Sum score for side effects of a questionnaire with 7 items, which could be rated on a scale from 0 (never) to 5 (very often). The x-axis is the same as that in Figure 4. There were no significant differences between the test conditions.
defects are carried out (43-56), eye movement recordings are needed to estimate how much eye movement has influenced the test results.

In summary, perimetry during ongoing eye movements induced by a moving fixation spot leads to results comparable to those of conventional perimeter. We found similar position, extent, and fluctuation of visual field defects with both methods in patients and also comparable positions and fluctuations of the blind spot in healthy control subjects. Fixation was within \( \pm 1^\circ \) of the visual field center during 97% of the perimetric testing time in patients and control subjects. The moving fixation spot did not lead to more stable test results or to fewer side effects, and it neither increased nor decreased the number of large saccades. Thus, moving the eyes has no significant effect on perimetry, leading us to conclude that rudimentary visual stimulus detection does not depend on eye movements.

REFERENCES

Anatomic Characteristics of the Ophthalmic and Posterior Ciliary Arteries

Senem Erdogmus, MD and Figen Govsa, MD

Background: There is little documentation of the course and relations of the ophthalmic artery (OA) and posterior ciliary arteries (PCAs).

Methods: The anatomic characteristics of the OA and PCAs were determined from a dissection of 19 neoprene-injected cadaver heads.

Results: The intraorbital OA had three segments, considering its relation to the optic nerve in the sagittal plane. The first segment extended from the point where the OA entered the orbit to its curving point. The second segment coursed superomedially from the inferolateral part of the optic nerve, crossing the optic nerve either superiorly or inferiorly. The third segment extended from the curving point of the superomedial distal portion of the second segment to the vessel’s termination. The OA was deviated at the junction of its first and second segments, defined as its “angle”; and at the junction of the second and third segments, defined as its “bend.” The PCAs arose from the first OA segment, the angle of the OA, the second OA segment and the OA bend. The patterns of branching of the PCAs were medial and lateral and medial, lateral, and superior. The superior PCA and the lateral PCA arose mainly from the angle of the OA, whereas the medial PCA arose from the curving point of the OA. The most frequently observed PCA pattern was a medial PCA and a lateral PCA. The average diameters of the medial PCA, the superior PCA, and the lateral PCA were 0.65, 0.48, and 0.68 mm, respectively. In all cases, pial arteries branching from the PCA and supplying the optic sheath were observed to form a vascular plexus on the optic sheath. The OA and PCAs were surrounded by a network of sympathetic nerves.

Conclusions: Because the most common pattern of PCAs is a medial and lateral branch, a surgical approach to the orbit from those directions carries a higher risk of damage to those vessels than a superior or inferior approach.


The superficial layers of the optic nerve head are supplied by the central retinal artery, and the deep layers are supplied by the posterior ciliary arteries (PCAs), branches of the ophthalmic artery (OA) (1–4). Ischemic disorders of the optic nerve head constitute an important cause of visual loss (3–7), spurring a search for methods to reliably evaluate the circulation to this tissue (3,4,7–9). Moreover, we have observed that the PCAs have a high risk of being damaged during surgery of the orbit. The aim of this study was, therefore, to investigate the precise anatomic characteristics of the OAs and PCAs.

METHODS

Dissection was performed on 19 adult male human cadavers (38 orbits), fixed with 10% formalin, in the Department of Anatomy, Faculty of Medicine, Ege University, Izmir, Turkey. After the skulls were opened and the brains were removed, a liquid latex 601 neoprene mixture colored with powder eosin paint was injected through the internal carotid artery. The orbital section of the frontal bone was removed by careful dissection, thus enabling the visualization of the orbital structures. A high-speed drill was used to remove the bony walls of the optic canal. After the removal of the bony walls and the connective fatty tissue of the orbit, the origin, position, branches, course, and anatomic relations of the PCAs were noted. Measurements in millimeters were made by means of a digital calliper. Statistical analyses were performed using SPSS version 10.0.

RESULTS

The Intraorbital OA

The course of the intraorbital part of the OA was macroscopically studied in three segments, considering its
FIG. 1. The posterior ciliary arteries (PCAs) in relation to the optic nerve and globe. 1, ophthalmic artery; 2, medial posterior ciliary artery (PCA); 3, lateral PCA; 4, superior PCA; 5, optic nerve; 6, globe; and 7, sympathetic nerves.

FIG. 2. The lateral posterior ciliary artery (PCA) originating from the angle part of the ophthalmic artery. 1, ophthalmic artery; 2, nasociliary nerve; 3, lateral posterior ciliary arteries (PCA); 4, optic nerve; 5, globe; 6, superior oblique artery; 7, sympathetic nerves; and 8, pial artery.

FIG. 3. The superior posterior ciliary artery (PCA) superior to the optic nerve. 1, superior PCA; 2, vascular network; and 3, sympathetic nerves.
relation to the optic nerve in the sagittal plane. The first segment extended from the point where the OA entered the orbit to its curving point. This first segment of the OA lay very close to the optic nerve, free of orbital fat. The OA usually ran along the inferolateral aspect of the optic nerve. The second segment of the OA began where the artery approached the lateral side of the optic nerve and started to cross over it at a right, acute, or obtuse angle. The point at which the artery changed direction and shape represented the end of the second segment. This second segment coursed superomedially from the inferolateral optic nerve, crossing the optic nerve either superiorly or inferiorly. In the third segment of the intraorbital OA, the vessel was located on the medial part of the optic nerve and globe, as well as the lateral part of the superior oblique and the medial rectus, reaching the medial wall of the orbit close to the anterior ethmoid foramen. The OA deviated at two points: at the junction of its first and second segments, defined as the “angle,” and at the junction of its second and third segments, defined as the “bend” (1,2). The OA angle was observed to be obtuse; the OA bend was not as well defined.

The PCAs

The PCAs arose independently from the first OA segment, the OA angle, the second OA segment, and the OA bend. The PCAs coursed distally, dividing into multiple branches and piercing the sclera close to the optic nerve medially, laterally, and superiorly (Figs. 1–3). The branching formations of the PCA are given in Table 1.

A medial PCA stemmed from various origins such as the first OA segment, the OA angle, the OA bend, and the third OA segment. The size of the outer diameter of the medial PCA is indicated in Table 2. The origin of the medial PCA is indicated in Table 3.

The lateral PCA arose from various origins, including the first OA segment, the OA angle, and the second OA segment, always lateral to the optic nerve (Fig. 1). The size of the outer diameter of the lateral PCA is given in Table 2.

The descriptive anatomy of the lateral PCA is given in Table 4.

Despite its various origins, including the OA angle, the second OA segment, and the OA bend, the superior PCA was always located superior to the optic nerve (Figs. 1 and 3). The size of the outer diameter of the superior PCA is given in Table 2. The descriptive anatomy of the superior PCA is summarized in Table 5.

In all cases, the intraorbital part of the OA and the PCA gave off thin pial arteries that penetrated the superior surface of the optic sheath at a right angle. These arteries formed a subpial meshwork. This network contributed to the vascularization of the optic nerve fibers (Figs. 2 and 3).

Also in all cases, the OA and PCAs were accompanied by fine nerve filaments and a plexus that seemed to arise from the carotid sympathetic nerves. These nerves surrounded and formed a network on the optic nerve sheath (Figs. 1–3).

DISCUSSION

Ophthalmic surgeons and neurosurgeons who operate within the confines of the orbit must know the neurovascular anatomy of the optic canal and, in particular, the course of the PCAs. This knowledge is especially relevant in the management of clinoidal meningiomas with intraorbital extension, aneurysms, hematomas, and optic sheath meningiomas with intracranial extension and as visualization of the operative field is restricted by orbital fat in strabismus surgery (10–12). Moreover, the origin and branching pattern of the PCAs cannot be defined on preoperative neuroimaging studies because of their small caliber. Surgical damage to the PCA circulation can result in a variety of ocular and optic nerve vascular disorders, causing varying degrees of visual loss (7). However, there have been few investigations discussing the detailed microsurgical anatomy of the PCAs.

| TABLE 1. Number and percentage of the posterior ciliary arteries |
|--------------------------|-----------------|-----------------|-----------------|-----------------|
|                | Branching Pattern | Right | Left | Bilaterally |
| Medial 1 lateral | 12 (63.15)       | 14 (73.7) | 11 (57.9) |
| Medial 1 superior | 7 (36.8)         | 5 (26.3) | 4 (21.05) |

Data are n (%).

| TABLE 2. Outer diameter of the posterior ciliary arteries |
|-------------------------------|-----------------|-----------------|
| Posterior ciliary artery      | Right           | Left            |
|                               | Diameter (mm)   | Diameter (mm)   |
| Medial                        | 0.65 6 0.12     | 0.65 6 0.14     |
|                              | (0.43–0.97)     | (0.41–0.90)     |
| Lateral                       | 0.68 6 0.11     | 0.67 6 0.14     |
|                              | (0.51–0.82)     | (0.43–0.78)     |
| Superior                      | 0.48 6 0.11     | 0.54 6 0.09     |
|                              | (0.34–0.65)     | (0.42–0.67)     |

Data are means (minimum–maximum).
TABLE 3. Number and percentage of the origin of the medial posterior ciliary artery arising from the ophthalmic artery

<table>
<thead>
<tr>
<th>Location of ophthalmic artery (OA) crossing of optic nerve</th>
<th>Top</th>
<th>Bottom</th>
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<tbody>
<tr>
<td>Site of origin</td>
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<td></td>
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<tr>
<td></td>
<td>n</td>
<td>%</td>
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<tr>
<td>First OA</td>
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<tr>
<td>OA angle</td>
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<td>OA bend</td>
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Previous authors describe the origins of the PCAs as variable (13–16). Some authors stated that the PCAs arose from the first part of the OA, others claimed that they arose superior to the optic nerve in the second part, and still others reported that they arose medial to the optic nerve (6,7,8,13–16). In this study, the superior PCA and the lateral PCA most frequently branched from the angle part of the OA, whereas the medial PCA originated from its bend part. Our results are most compatible with those of Hayreh (7), Ettl et al (9), and in particular Onda et al (8). Sudakevitch (15) reported that the medial PCA, in common with the central retinal artery, was usually the first branch of the OA, that the lateral PCA was the second, and that both PCAs arose before the lacrimal artery, which was situated at the OA angle. As opposed to Sudakevitch, we have observed the medial PCA to arise independently from the OA.

In their studies, previous authors have found that an eye might be supplied by one (in 3%–7%), two (in 25%–48%), three (in 39%–50%), four (in 8%–17%), or five (in 2%–8%) PCAs arising from the OA (13–16). The most frequently observed branching pattern was the one for which there were one medial and one lateral PCAs. This study was in agreement with the observations in previous studies (1,7,9) with regard to the existence of two PCA branches in most cases. However, in less than one third of the cases, there were three branch PCA, a finding that differs markedly from those of Lang and Kageyama (16) and Ducournau (17).

TABLE 4. Number and percentage of the origin of the lateral posterior ciliary arteries arising from the ophthalmic artery

<table>
<thead>
<tr>
<th>Location of ophthalmic artery (OA) crossing of optic nerve</th>
<th>Top</th>
<th>Bottom</th>
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<tbody>
<tr>
<td>Site of origin</td>
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Previous authors have reported the intraorbital presence of the autonomic fibers arising from the internal carotid plexus (10,18). We have observed this neural network to arise from the intracranial sympathetic nerve fibers on the internal carotid artery and accompany the OA and PCAs, forming a network on the optic sheath. These fibers are thought to control blood supply to the intraorbital tissues and should be avoided during surgery (10,18,19).
TABLE 5. Number and percentage of origin of the superior posterior ciliary arteries arising from the ophthalmic artery

<table>
<thead>
<tr>
<th>Location of ophthalmic artery (OA) crossing of optic nerve</th>
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REFERENCES

PHOTO ESSAY

Suprasellar Hemangioblastoma

Shiro Miyata, MD, Takeshi Mikami, MD, Yoshihiro Minamida, MD, Yukinori Akiyama, MD, and Kiyohiro Houkin, MD

Abstract: A 59-year-old woman presented with disturbance of consciousness and decreased visual acuity caused by a suprasellar mass identified on MRI. A bifrontal interhemispheric approach allowed removal of the top and lateral sides of the tumor from the wall of the third ventricle. The hypothalamus appeared to be the origin of the mass, which proved to be hemangioblastoma, a rare tumor in this location.


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A 59-year-old woman complained of general fatigue, loss of volition, and decreased vision in July 2004 when she was admitted to our neurosurgical department. She was somnolent, and her recent memory was impaired. Karnofsky performance status was 50%. Best-corrected visual acuity was 20/300 in both eyes.

MRI revealed a 3.5-cm globular lesion, with small cystic structures, that was isointense to brain parenchyma on precontrast T1 and hyperintense on T2 MRI. The tumor was located in the third ventricle and displaced the left cerebral peduncle dorsally. Postcontrast T1 MRI showed marked enhancement and the fact that the mass had a discrete border (Fig. 1A–B). Cerebral angiography demonstrated a tumor stain supplied by both superior hypophyseal arteries (Fig. 1C).

Surgery was performed via the bifrontal interhemispheric approach. The lamina terminalis was incised above...
the optic chiasm, and then an easily bleeding reddish mass with a smooth surface and clear border with the surroundings was found in the third ventricle (Fig. 1D). The top and lateral sides of the tumor were easily peeled from the wall of the third ventricle. Accordingly, the hypothalamus at the base of the third ventricle was considered the tumor origin. With repetitive coagulation, the tumor was removed piece by piece.

Histopathologically, the tumor had numerous capillary vessels, each composed of a single layer of endothelial cells without nuclear heteromorphism (Fig. 2). The tumor had two main components of large vacuolated stromal cells and a rich capillary network. Immunostaining revealed that the tumor had endothelium-specific markers CD31 and CD34. The histologic diagnosis was hemangioblastoma.

Postoperatively, the patient had no deterioration of neurologic deficits other than panhypopituitarism. MRI during the follow-up period demonstrated total removal of the tumor and no recurrence for at least the 3 years of follow-up.

Hemangioblastoma is a benign tumor of uncertain histogenesis and accounts for 2.6% of all brain tumors. It is likely to occur predominantly in the cerebellar hemisphere, spinal cord, and medulla oblongata of adults 30–40 years of age (1). Hemangioblastoma arising from supratentorial locations is rare, and hemangioblastoma arising from the suprasellar region is even rarer.

The most frequent symptoms of patients with suprasellar hemangioblastomas are visual and hormonal disturbances (2-9). MRI is the diagnostic study of choice (8), although angiographic study is also useful in revealing a highly vascularized lesion with a persistent blush (2).

It may be difficult to histopathologically differentiate hemangioblastoma from angioblastic meningioma and metastatic renal cell carcinoma. The histologic features of these tumors are similar (2-4). Angioblastic meningioma is usually supratentorial, solid, and attached to the dura, whereas hemangioblastoma is usually cystic with a mural nodule, lacks dural attachment, and is exceedingly rare in the supratentorial region. The difficulty in distinguishing hemangioblastoma from metastatic renal cell carcinoma arises because the arrangement of its stromal cells appears epithelioid and resembles the clear cell type of renal cell carcinoma.

REFERENCES
Dilated Superior Ophthalmic Veins and Posterior Ischemic Optic Neuropathy After Prolonged Spine Surgery

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FIG. 1. Postcontrast T1 axial (A) and coronal (B) orbit MRI studies performed 19 hours after prolonged prone position lumbar spine surgery show markedly dilated superior ophthalmic veins. Five months after the surgery, axial (C) and coronal (D) studies show normalization in the caliber of the superior ophthalmic veins.

Abstract: A 55-year-old man developed bilateral posterior ischemic optic neuropathy after prolonged prone position lumbar laminectomy. Brain MRI performed 19 hours after the procedure revealed markedly dilated superior ophthalmic veins, a finding that had disappeared on a comparable study performed 5 months later. This first report of dilated superior ophthalmic veins present in the immediate postoperative period but not later may be important in suggesting that an increase in orbital venous pressure during surgery contributes to the development of postoperative posterior ischemic optic neuropathy (PION).


A 55-year-old man underwent a 4.5-hour but otherwise uncomplicated lumbar laminectomy for lumbar stenosis in the prone position and complained of painless decreased vision in both eyes upon recovery from anesthesia. He had had an estimated blood loss of 900 mL and a postoperative hemoglobin of 11.6 g/dL. He had required 3600 mL of crystalloid and 500 mL of colloid and had had an intraoperative urine output of 200 mL. The lowest recorded intraoperative blood pressure had been 90/50 mmHg. His medical history included fibromyalgia, chronic fatigue, gout, sleep apnea, degenerative joint disease, peripheral neuropathy, benign prostatic hypertrophy, atherosclerosis, and previous lumbar spine surgery. He had undergone coronary artery bypass surgery 1 year earlier.

On the first postoperative day, visual acuity was counting fingers in the right eye and hand movements in the left eye. There was no facial edema. Confrontation visual fields confirmed dense central scotomas bilaterally. Color vision tested with Ishihara pseudoisochromatic plates was absent in each eye. Pupils measured 3.5 mm in dim
illumination and constricted sluggishly to light without a relative afferent pupillary defect. Ophthalmoscopic examination revealed normal optic discs. The retina appeared normal without venous dilation. We made a presumptive diagnosis of bilateral posterior ischemic optic neuropathy (PION) and attributed it to prolonged prone position spine surgery.

Brain MRI performed 19 hours after the procedure surprisingly revealed dilated superior ophthalmic veins (Fig. 1A–B) on each side with no compressive lesions and no optic nerve enhancement. There was no suggestion of intracranial hypotension or engorgement of the dural venous sinuses. The cavernous sinuses were normal. One day later, visual evoked potentials showed no responses from either eye.

Examination 4 weeks later revealed diffusely pale optic discs without cupping in both eyes. Visual acuity had improved to 20/25 in the right eye and 20/20 in the left eye, but with severely constricted visual fields on automated perimetry. Otherwise the neuro-ophthalmologic examination remained unchanged.

Repeat MRI of the brain and orbits 5 months postoperatively showed normal caliber of the superior ophthalmic veins (Fig. 1C–D). There was no clinical evidence of an arteriovenous fistula and results of brain magnetic resonance venography (MRV) were normal.

Hemodynamic derangements in arterial perfusion pressure, orbital venous pressure, and blood oxygen-carrying capacity are thought to be key factors in the development of postoperative PION (1,2). Of these three factors, increased orbital venous pressure is the most difficult to document, and therefore its role in the pathogenesis of PION has been the most difficult to ascertain. The prone position, jugular vein ligation, increased cerebrospinal fluid (CSF) pressure, orbital edema, and the Trendelenburg (dependent head) position have all been implicated as factors that could lead to increased orbital venous pressure (3–12). To our knowledge, this is the only patient with postoperative PION to demonstrate dilated superior ophthalmic veins on MRI in the acute setting and a reduction in venous caliber over time, suggesting an association between an increase in orbital venous pressure during surgery and the development of PION. A study of the effect of prolonged prone positioning on the caliber of the superior ophthalmic veins might help determine whether increased orbital venous pressure plays a role in postoperative PION.

REFERENCES
HYPOTHESIS

Saccadic Burst Cell Membrane Dysfunction Is Responsible for Saccadic Oscillations

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Abstract: Saccadic oscillations threaten clear vision by causing image motion on the retina. They are either purely horizontal (ocular flutter) or multidimensional (opsoclonus). We propose that ion channel dysfunction in the burst cell membrane is the underlying abnormality. We have tested this hypothesis by simulating a neuromimetic computational model of the burst neurons. This biologically realistic model mimics the physiologic properties and anatomic connections in the brainstem saccade generator. A rebound firing after sustained inhibition, called post-inhibitory rebound (PIR), and reciprocal inhibition between premotor saccadic burst neurons are the key features of this conceptual scheme. PIR and reciprocal inhibition make the circuits that generate the saccadic burst inherently unstable and can lead to oscillations unless stabilized by external inhibition. Our simulations suggest that alterations in membrane properties that lead to an increase in PIR, a reduction in external glycinergic inhibition, or both can cause saccadic oscillations.


DISORDERS OF SACCADES AFFECTING STEADY FIXATION

A fundamental requirement for clear vision is stabilization of the image of an object on the retina. Steady fixation is threatened by spontaneous abnormal eye movements, which include nystagmus, saccadic dysmetria, and saccadic intrusions (1).

Nystagmus is characterized by drift of the eyes away from the desired target that is usually followed by a corrective saccade (quick phase) back to the target of interest. In saccadic dysmetria, the eyes overshoot or undershoot the target, such that a corrective gaze movement is required to bring the eyes to fixation of the new target. When the hypermetria is extreme, large saccades, separated by an intersaccadic interval, move the eyes back and forth around the fixation point. Such eye movements are called macrosaccadic oscillations.

Saccadic intrusions, or uncalled-for saccades occurring when fixation is desired, include square-wave jerks (SWJ), macro square wave jerks (macro SWJ), saccadic pulses, and saccadic oscillations. SWJ are pairs of small horizontal saccades (<2 degrees), one away and one back to the target of interest, separated by a 200-ms interval. SWJ often occur in series. Macro SWJ are not simply enlarged SWJ but are pairs of large saccades, the first away from and the second back to the target, separated by a short (75–150 ms) interval (1). Saccadic pulses are brief; small eye movements away from the target followed by a rapid drift back to an object of interest. Unlike SWJ, saccadic pulses lack a step change in innervation to hold the eyes in a new position, and the eyes come back to the object of interest by a relatively fast drift (1).

Saccadic Oscillations

Saccadic oscillations consist of continuous uncalled-for back-to-back saccades without an intersaccadic interval. They are called ocular flutter when purely horizontal and opsoclonus when multidimensional (2–4). Saccadic oscillations occur most commonly in paraneoplastic syndromes, postinfectious encephalitis, and demyelinating disorders, in which the underlying etiology is thought to be an...
autoimmune or cross-immune mechanism (1,5). Saccadic oscillations may also occur in healthy subjects, as a physiologic phenomenon during eye closure and with convergence (6,7). Saccadic oscillations can be familial (4), caused by drug or other intoxications (8,9), associated with migraine (2), or transiently present in the newborn (10).

We propose that alterations in the properties of the membranes of burst neurons underlie saccadic oscillations. We test this hypothesis by simulating a neuromimetic computational model of the burst neurons. A neuromimetic model is one that implements physiologically realistic parameters of the biophysical properties of the membranes of neurons within an anatomically realistic circuit.

The concept of a membrane-based etiology of saccadic oscillations stems from the characteristics of the neural connections in the brainstem saccade generator. Therefore, we will first outline the functional features of the central areas that generate saccades and that are the cause of saccadic oscillations in pathologic circumstances. Then we will demonstrate how a neuromimetic model with its membrane-based hypothesis explains saccadic oscillations (2,4,8,9).

Functional Organization of a Neural Circuit That Generates Saccades and Saccadic Oscillations

Voluntary saccades are initiated by circuits within the frontal eye field (FEF) and parietal eye field (PEF) in the cerebral cortex. Saccade-related signals from the cerebral cortex follow two main pathways as schematized with the blue and brown arrows in Fig. 1. One of these pathways (blue arrows) projects to the nucleus reticularis tegmenti pontis (NRTP) of the pontine reticular formation. The other pathway (brown arrows) projects to the superior colliculus (SC). Neurons of NRTP then project to the oculomotor vermis (OMV) (lobules 5–7) of the cerebellar cortex that sends GABAergic inhibitory signals to the underlying caudal fastigial nucleus (fastigial oculomotor region [FOR]). The FOR projects to the omni directional pause neurons (OPN) of the saccadic burst generator area in the nucleus raphe interpositus of the midline pons (11,12) as well as to the burst neurons themselves (not shown for clarity). The OPN also receive parallel projections directly from the SC (brown arrow in Fig. 1). Excitatory burst neurons (EBN), located in the caudal pontine reticular formation, and inhibitory burst neurons (IBN), located in the nucleus paragigantocellularis dorsalis in the medulla, receive inhibitory projections from OPN. A key role of the OPN is to maintain sustained inhibition of EBN and IBN when steady fixation is required. When a rapid shift of gaze (saccade) is warranted, inhibition of the OPN upon the EBN and IBN is removed suddenly, causing a rebound increase in the firing rate of these burst neurons. Postinhibitory rebound (PIR) is a rebound increase in neuronal membrane discharge after sustained membrane hyperpolarization. Although hypothetical, such a rebound burst in discharge would help saccades by contributing to their fast movement (13,14).

EBN and IBN are the critical neurons in the generation of saccades and are schematized in Figure 1 as “E” and “I,” respectively. The EBN project directly to the ipsilateral sixth cranial nerve nucleus, where they synapse upon motoneurons and internuclear neurons (green excitatory projections in the schematic diagram of Fig. 1). The internuclear neurons of the sixth cranial nerve nucleus project to the medial rectus subgroup of the contralateral third cranial nerve nucleus (schematized by green excitatory projections crossing the midline in Fig. 1). Hence, for rightward saccades, the excitatory burst of activity reaches the right sixth cranial nerve nucleus and left third cranial nerve nucleus motoneurons from EBN on the right side. The IBN, which project to the contralateral abducens nucleus, are normally inhibited by the OPN and the contralateral IBN. For a rightward saccade, the right side (ipsilateral) IBN are released from inhibition and then inhibit the contralateral sixth cranial nerve motoneurons (red inhibitory projection). The latter innervate the antagonistic extraocular muscles (schematized as red projections in Fig. 1). The ipsilateral IBN also project to the contralateral IBN, presumably to prevent them from becoming active (via rebound after OPN disinhibition) and inhibiting the agonist premotor and motor neurons (15). The reciprocal inhibition across the midline between two IBN populations (with PIR) forms a neural circuit with a positive feedback loop. This feedback loop is unstable if the strengths of the connection around the loop are too strong and could lead to high-frequency saccadic oscillations, such as ocular flutter (4,15). During steady fixation, oscillations that may emerge from the inherently unstable burst neuron network are prevented by inhibition from the OPN.

Hypothesis for Saccadic Oscillations

We propose a mechanism intrinsic to the neurons that generate saccadic bursts (4) (Fig. 1). In particular, we propose that saccadic oscillations arise from the instability in the saccadic burst neuron circuit because of an imbalance between burst neuron excitability and external inhibition. Such an imbalance might arise from an abnormal increase in burst neuron excitability, reduced external inhibition, or increased amplitude of PIR. The PIR is a rebound increase in neuronal membrane discharge after sustained membrane hyperpolarization. Maximal conductance through pacemaker ion channels, including hyperpolarization-activated, inward-mixed, cation currents (I_h) and low threshold
FIG. 1. The neural circuit that generates saccades. Saccades are initiated by activity in neurons of the frontal and parietal eye fields of the cerebral cortex. These signals then follow two pathways projecting to the nucleus reticularis tegmenti pontis (NRTP) of the pontine reticular formation and the superior colliculus (SC). The NRTP sends projections to the oculomotor vermis (OMV) (lobules 5–7) of the cerebellar cortex which, in turn, sends GABAergic inhibitory signals to the underlying caudal fastigial nucleus (fastigial oculomotor region [FOR]; gray box is the cerebellum). The FOR projects to the omnidirectional pause neurons (OPN) of the saccadic burst generator area in the nucleus raphe interpositus of the midline pons. Excitatory burst neurons (EBN) and inhibitory burst neurons (IBN) receive inhibitory projections from OPN. The OPN have a key role in maintaining sustained inhibition of the EBN and IBN when steady fixation is required. When a rapid shift of gaze is needed, OPN-triggered inhibition on the EBN and IBN is suddenly removed, causing a rebound increase in the firing rate of these neurons. The EBN project directly to the ipsilateral abducens nucleus (VIth nucleus), where they synapse upon abducens motoneurons (mn) and internuclear neurons (in) (green excitatory projections). The internuclear neurons of the abducens nucleus project to the medial rectus subgroup of the contralateral oculomotor nucleus (IIIrd nucleus) (see green excitatory projections crossing the dashed midline). Hence, for making rightward saccades, the excitatory burst of activity reaches the right abducens and left IIIrd nerve nucleus motoneurons from EBN in the right paramedian pontine reticular formation (PPRF). The right side (ipsilateral) IBN, which receives inhibitory inputs from OPN and the left (contralateral) IBN, projects to the contralateral (left) abducens nucleus, inhibiting the abducens motoneurons that innervate the antagonistic muscles.
calcium currents \( (I_T) \), determines neural excitability and the amplitude of PIR (16-18) (Fig. 2). Although PIR has yet to be directly identified in excitatory and inhibitory burst neurons, the necessary ion channels for carrying currents generating PIR \( (I_h \text { and } I_T) \) have been identified in human saccadic burst neurons (19).

We hypothesize that increases in neural excitability and/or in PIR due to pathologically increased \( I_h \) and/or \( I_T \) reduce the effects of external inhibition so that saccadic oscillations can emerge. Alternatively, a reduction in external inhibition because of malfunction of the strychnine-sensitive glycine receptors could also cause saccadic oscillations.

Testing the Hypothesis: A Neuromimetic Model of Saccadic Oscillations

We have simulated a neuromimetic model of saccade generation with physiologically realistic membrane properties to test this hypothesis (4,15). This neuromimetic model is consistent with anatomic organization of saccadic burst neuron circuits and is based on the traditional local feedback burst neuron model (red is inhibitory and green is excitatory local feedback as schematized in Fig. 3A) (14,20–24). When membrane parameters are in the physiologic range, the model produces saccades with normal amplitudes and velocities. When the neural excitability in the model is increased by altering membrane parameters consistent with increased \( I_h \) and/or \( I_T \) or by reducing the effects of the external inhibition, the simulation produces saccadic oscillations without any assumed structural alterations. The anatomic framework of the neuromimetic model is illustrated in Figure 3A. Excitatory and inhibitory burst neurons send local feedback projections (red inhibitory and green excitatory pathways as schematized in Fig. 3A) implementing the reciprocal inhibition necessary to generate accurate yet high-velocity saccades. The saccadic burst neuron and its membrane properties that play a key role are illustrated in Fig. 3B (see reference 15 for model methodology details).

Consistent with the anatomic and physiologic architecture of the neural network that generates saccades (25), this model has a short-latency negative feedback loop around a high-gain amplifier (built into the burst neurons) (yellow box and blue pathway in Fig. 3A–B). When a saccade is called for, this feedback loop generates a burst of neural discharge proportional to the eye velocity and produces a saccade of the correct amplitude and duration. However, because of the inherent high gain (neural discharge rate per unit amplitude of the desired eye displacement), the position error signal of the burst neurons, and the possible delay in the feedback loop, this system is prone to oscillate (4,15,20). Because of the high gain of the output nonlinearity of the burst neurons for small or null desired eye movement, this feedback system can oscillate even when there is a small input such as a small spontaneous saccade, unless it is suppressed by adequate inhibition from OPN. In other words, when burst neuron excitability and OPN inhibition are balanced, the saccadic system remains stable. Either an increase in neural excitability or a reduction of OPN inhibition can cause instability and oscillations. One way to increase the gain is to increase the amplitude of PIR due to increased membrane excitability.

This hypothesis raises an important question. Does PIR exist in saccadic burst neurons? PIR appears to be the property of many neurons that must develop a prompt increase in their discharge after inhibition (26–28). PIR is known to occur at the offset of hyperpolarization and is mediated by \( I_T \) carried by Cav3.1, Cav3.2, and Cav3.3 calcium channels and \( I_h \) carried by HCN1, HCN2, HCN3, and HCN4 channels (16). Human saccadic burst neurons express these subtypes of ion channels carrying \( I_T \) and \( I_h \) (19). A burst discharge due to PIR after marked hyperpolarization could occur in the paramedian pontine reticular formation (PPRF) burst neurons owing to their low membrane threshold voltage. Further, with this biophysical property, a single neuron is capable of firing at high rates automatically and without stimulation when released from inhibition (4,13,14). The strong PIR could be attributed to the increased activation (increase in maximal conductance) of specific subtypes of ion channels carrying \( I_T \) and/or \( I_h \).

Correlates of PIR in the Neuromimetic Model

In vivo and in vitro electrophysiology experiments from neurons with PIR suggest that the membrane time constant \( (mTc) \) (Fig. 3B) and neural response gain \( (EBN \text { gain}) \) (Fig. 3B) are determined by the strength of ion currents, including \( I_h \) and \( I_T \) (16-18,29-31). Ion channel activation kinetics (for \( I_h \) and \( I_T \) currents) and maximal conductance through these ion channel subtypes (and therefore the amplitude of PIR) were simulated by adjusting the neuronal \( mTc \) and neuronal membrane excitability \( (EBN \text { gain}) \). Indeed, \( mTc \) and burst neuron gain are the key determinants of the amplitude and the frequency of resultant saccadic oscillations (Fig. 4). Figure 4 illustrates that an increase in the burst neuron gain (i.e., increasing \( I_h \) and \( I_T \) conductance to increase neural excitability and PIR) causes an increase in the frequency (Fig. 4A) and amplitude (Fig. 4B) of oscillations. Furthermore, the frequency is also determined by the value of \( mTc \). A shorter \( mTc \) (faster membrane kinetics) simulates a higher oscillation frequency.
FIG. 2. The influence of currents on the strength of postinhibitory rebound (PIR). A. Schematic diagram of the normal physiologic state. \( I_h \) is a pacemaker conductance activated by a hyperpolarizing membrane potential (in the figure, \( I_h \) activates below membrane threshold). This inward cationic conductance further depolarizes the membrane. Notice the direction of the arrow in the figure. At approximately 60 mV membrane potential, \( I_h \) gradually ceases and \( I_T \) begins to activate. \( I_T \) further depolarizes the membrane until a sodium conductance \( (I_{Na}) \) mediates a burst of action potential spikes. This burst of spikes characterizes normal PIR. B. Schematic diagram of the state when \( I_h \) or \( I_T \) increases beyond physiologic limits. As \( I_h \) and/or \( I_T \) increase, the membrane depolarizes faster. Notice thicker arrows in this panel and a steeper slope of the membrane potential compared with the gray line in A. In this situation, action potential spikes are also more frequent and thus PIR is stronger. C. Illustration of a state when \( I_h \) and/or \( I_T \) are decreased below their physiologic limits. When \( I_h \) and/or \( I_T \) are weaker, the rate of membrane potential depolarization is relatively slower. Compare the shallower slope of membrane depolarization to the gray line in C. Hence the action potential spikes are less frequent, reflecting a weaker PIR. Black traces represent membrane potential. Lower arrows represent hyperpolarization activated inward cation currents \( (I_h) \). Upper arrows are low threshold calcium currents \( (I_T) \). The dashed line represents the membrane threshold.

HOW THE MEMBRANE HYPOTHESIS EXPLAINS SACCADIC OSCILLATIONS FROM VARIOUS UNDERLYING CAUSES

Saccadic oscillations have been observed in patients with cocaine abuse and with strychnine poisoning, yet there is no apparent structural abnormality in their central nervous systems (1). We use the neuromimetic model to explain the saccadic oscillations reported in these patients. Cocaine reduces norepinephrine reuptake, causing elevation in its synaptic levels (32). Norepinephrine increases \( I_h \) conductance (33). Thus cocaine intoxication may cause saccadic oscillations by increasing the PIR and burst neuron excitability because of the increase in \( I_h \) conductance through the burst neuron membrane. Saccadic oscillations are reportedly associated with hyperammonemic and uremic states, although quantitative recording confirming the exact pattern of oscillations is lacking (1). The pH of the brain changes in such toxic states. Extracellular pH regulates the maximal \( I_h \) conductance (29). Thus, increased neural excitability due to increased \( I_h \) may cause saccadic oscillations in hyperammonemic and uremic states. Opsoclonus also is reported in hyperosmolar states. Perhaps this phenomenon is related to the effects of the osmolarity of the extracellular fluid on ion channel function. For example, the concentration of extracellular sodium influences the maximal conductance through the \( I_h \) channel (29).

Opsoclonus resulting from organophosphate poisoning may be the consequence of cholinergic excess causing an increased activation in the FOR (34). The FOR is incorporated in a feedback loop of the brainstem saccade generator. Therefore, hyperexcitability of the FOR could lead to instability of the saccadic burst generators by influencing their membrane excitability, causing saccadic oscillations (35–37). Saccadic oscillations are also associated with migraine (2). An inherent hyperexcitability is thought to underlie some of the physiologic disturbances in migraine (38,39). Hence, it is possible that microsaccadic oscillations associated with migraine are due to increased burst neuron excitability. Strychnine poisoning is known to cause saccadic oscillations. Strychnine blocks glycine channels. This blockade may manifest as decreased OPN inhibition on the burst neuron membrane, which could cause saccadic oscillations.

We also speculate that in addition to direct autoimmune damage to cerebellar Purkinje neurons and neurons in the brainstem saccade generators, paraneoplastic, and postinfectious opsoclonus could also be due to the autoimmune or cross-immune reaction to the ion channels or their modulators in burst neuron. The membrane hypothesis for saccadic oscillations can also explain why some subjects can generate voluntary nystagmus, which is a transient saccadic oscillation usually associated with convergence.
FIG. 3. The saccade generator. A. The premotor network. The excitatory burst neurons (EBN) and inhibitory burst neurons (IBN) send local feedback projections that implement reciprocal inhibition for generating accurate and high-velocity saccades. OPN, omnipause neurons; yellow box: feedback gain. B. The model burst neuron membrane. The short latency negative feedback loop is schematized as a blue arrow with a yellow box. This loop is around a high-gain (k) amplifier built into the burst neurons. Although the gain of the negative feedback loop around the burst neuron circuit determines the amplitude of the saccade, the delay time is not the main determinant of the frequency of saccadic oscillations. (Red lines indicate inhibitory projections. Green lines indicate excitatory projections. The blue line indicates feedback projection.)
We speculate that an individual’s specific complement of ion channel subtypes in the brainstem circuits that generate saccades influences the ability to voluntarily generate these oscillations as well as their dynamic characteristics. This innate ability would be under genetic influence and may explain why a relatively wide range of frequencies of physiological saccadic oscillations are seen across normal individuals (15) but that within families, the frequency of voluntary nystagmus and saccadic oscillations is similar (4,40). Carbamazepine, a calcium channel antagonist (41), is reported to ameliorate saccadic oscillations (42). The membrane-based mechanism of saccadic oscillations can explain this effect of carbamazepine.

**CONCLUSION**

We hypothesize that, regardless of the primary cause, ocular flutter and opsoclonus are related to alterations in the membrane properties of the neurons that generate saccadic bursts. We also propose that the level of activity in OPN may play a role in the genesis of saccadic oscillations. However, the properties of the oscillations and the ease with which the system can be made to oscillate depend critically on membrane properties of the burst neurons. Finally, our hypothesis suggests novel approaches to the treatment of ocular flutter and opsoclonus. Selective ion channel blockers may offer therapeutic benefits. Alternatively, counterintuitive therapy, interfering with the function of a normal ion channel to decrease membrane excitability in the face of increased excitability or impaired external inhibition, may reduce oscillatory behavior.

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Daniel M. Jacobson, MD completed neurology training at the University of Pittsburgh and neuro-ophthalmology fellowship at the University of Iowa. He joined the staff of the Marshfield Clinic in Marshfield, Wisconsin in the Departments of Neurosciences and Ophthalmology in 1987 with a faculty appointment at the University of Wisconsin. During a 16-year period at the Marshfield Clinic, he cared for thousands of patients and authored more than 50 scientific manuscripts in the field of neuro-ophthalmology. He was honored with numerous teaching and research awards and recognized for his ability to apply basic science principles to the investigation of the most pressing clinical issues. The Marshfield Clinic Foundation has established a memorial fund in his name. In recognition of the profound impact he has had on the field of neuro-ophthalmology, the North American Neuro-Ophthalmology Society (NANOS) has established a lecture to be presented each year at the NANOS meeting.

Familial Idiopathic Intracranial Hypertension

James J. Corbett, MD

Background: Case reports of familial idiopathic intracranial hypertension (IIH) have appeared sporadically and infrequently.

Methods: We reviewed the medical records of all patients with IIH seen at our institution to identify the number of familial cases.

Results: Out of a cohort of 237 patients with IIH, we identified 27 members (25 women and 2 men) from 11 families, with IIH usually self-reported or reported by the index case. In 7 of the 11 families, the relationship was parent to child; in 4, it was sibling. Obesity was present in 85% of the family members.

Conclusions: Familial IIH appears to be more common than reported previously. A systematic evaluation of first-degree relatives may help to identify more cases. A study of the patterns of inheritance and associated co-morbidities may result in better understanding of the genetic issues with this disorder.

The medical records of the index case and all available family members were reviewed for the following variables: age at onset, body habitus preferably as body mass index (BMI) (22), and associated conditions, including psychiatric.

Papilledema was graded using the Frise\'n scale (23). The results of brain CT or MRI were included where available.

**RESULTS**

We identified 254 patients with ICP greater than 250 mm water. Of these, 17 patients were excluded because of secondary causes of raised ICP identified by history or physical examination. We included 237 patients in the final analysis. Of these, 219 had papilledema and 18 did not. There were 11 families consisting of 27 members with a family history of IIH (Table 1).

**Family 1:**
Mother and 4 Daughters
All family members except the youngest daughter (BMI 38 kg/m$^2$) were extremely obese (BMI >40 kg/m$^2$) and had headache and papilledema grade I–II. The cerebrospinal fluid (CSF) opening pressure (OP) was greater than 250 mm water in all except two individuals (OP 220 mm water). The family came to our attention when two of the family members who accompanied the index case (25-year-old daughter) informed us that they were having similar symptoms. The optic disc photographs of this family are presented in Figure 1.

**Family 2:**
Heterozygous Twin Sisters
Both were symptomatic of IIH at the age of 15 with chronic daily headache, were extremely obese (BMI >40 kg/m$^2$) and had metabolic syndrome. Both had grade II–III papilledema and Chiari I malformations. Although OP was elevated in one (325 mm water), LP in the other was not attempted because of the Chiari malformation. Interestingly, bipolar disorder was diagnosed in both sisters.

**Family 3:**
Two Sisters
Both had chronic headache and were obese (BMI >30 kg/m$^2$). The older one was referred by an optometrist who had incidentally discovered papilledema, and she revealed that she was the older sister of the index case who was an established patient. They had grade III papilledema and grade I papilledema, respectively. OP was 340 mm water in one and “elevated” per radiologic findings in the other.

**Family 4:**
Mother and Two Daughters
The mother was identified at our clinic at age 59 and had received the diagnosis of IIH at age 31 elsewhere with elevated CSF pressure. She subsequently underwent multiple CSF shunt procedures. Despite these, she became legally blind. She recently died of respiratory complications related to extreme obesity (BMI >60 kg/m$^2$). IIH was diagnosed in both daughters at age 15. Both were extremely obese (BMI >40 kg/m$^2$) and complained of chronic headaches and transient visual obscurations (TVO). One of the daughters had no papilledema and no formal OP although the radiologist believed the OP was high, and the other daughter had low-grade papilledema. All three family members had a radiographic empty sella turcica, and both daughters had a psychotic disorder.

**Family 5:**
Mother and Daughter
The index case was the daughter who presented at age 21 and was obese (BMI 37 kg/m$^2$) with headache and grade III papilledema. OP was 400 mm water, and she had a radiographically empty sella turcica. She reported that her mother had also been found to have a radiographically empty sella turcica and was subsequently found to have elevated CSF pressure. Curiously, her mother had initially presented to an otolaryngologist with CSF rhinorrhea.

**Family 6:**
Mother and Two Daughters
The index case was the older sister who presented at age 39 with headache, tinnitus, and blurred vision. She had a BMI of 44 kg/m$^2$ and grade V papilledema. OP was 440 mm water. IIH had been diagnosed in her 52-year-old mother in her 30s and had been treated with acetazolamide. The mother’s medical records could not be located. IIH was also diagnosed by a neuro-ophthalmologist in the younger sister, a nurse in Chicago, in her 30s. We spoke to her by telephone, but she could not obtain her medical records.

**Family 7:**
Mother and Daughter
The index case was the daughter with the diagnosis of IIH at age 20. She presented with headache and bilateral grade I papilledema. OP was 390 mm water. She had a radiographically empty sella turcica. She mentioned that her mother also had headache and was told that she had a radiographically empty sella turcica.
TABLE 1. Familial cases of idiopathic intracranial hypertension identified at the University of Mississippi Medical Center between 1990 and 2007

<table>
<thead>
<tr>
<th>Family</th>
<th>Relationships of Family Members with IIH</th>
<th>Age at Diagnosis (years)</th>
<th>Habitus (BMI†)</th>
<th>Presenting Symptom</th>
<th>Lumbar Puncture Opening Pressure (mm Hg)</th>
<th>Brain MRI/CT Findings</th>
<th>Papilledema description or Frisen Grade</th>
<th>Associated Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mother and 4 daughters</td>
<td>25</td>
<td>Obese (47)</td>
<td>Headache</td>
<td>420</td>
<td>Partially empty sella</td>
<td>I</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>47</td>
<td>Obese (45)</td>
<td>Headache</td>
<td>220</td>
<td>Normal</td>
<td>II</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16</td>
<td>Obese (43)</td>
<td>Headache</td>
<td>270</td>
<td>Normal</td>
<td>I</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18</td>
<td>Obese (46)</td>
<td>Headache</td>
<td>220</td>
<td>Normal</td>
<td>I</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
<td>Obese (38)</td>
<td>Headache</td>
<td>290</td>
<td>Normal</td>
<td>I</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Heterozygous twin sisters</td>
<td>15</td>
<td>Obese (53)</td>
<td>Headache</td>
<td>325</td>
<td>Chiari I malformation</td>
<td>III</td>
<td>Manic psychosis Depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>Obese (45)</td>
<td>Headache</td>
<td>Dry tap</td>
<td>Chiari I malformation</td>
<td>II</td>
<td>Depression</td>
</tr>
<tr>
<td>3</td>
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<td>26</td>
<td>Obese (42)</td>
<td>Headache</td>
<td>Elevation 940</td>
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<td>III</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
<td>28</td>
<td>Obese (55)</td>
<td>Incidental</td>
<td>Elevation 340</td>
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<td>I</td>
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<tr>
<td>4</td>
<td>Mother and 2 daughters</td>
<td>31</td>
<td>Obese (61)</td>
<td>Headache</td>
<td>420</td>
<td>Empty sella</td>
<td>Moderate</td>
<td>Diabetes mellitus Psychosis, diabetes mellitus</td>
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<td>16</td>
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<td>Headache</td>
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<tr>
<td></td>
<td></td>
<td>15</td>
<td>(62)</td>
<td>Headache</td>
<td>Elevation 340</td>
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<td>5</td>
<td>Mother and daughter</td>
<td>21</td>
<td>Obese (38)</td>
<td>Headache</td>
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<td>Normal</td>
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<td>—</td>
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<td></td>
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<td>47</td>
<td>Obese</td>
<td>CSF rhinorrhea</td>
<td>Elevation 340</td>
<td>NR</td>
<td>NR</td>
<td>—</td>
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<td>6</td>
<td>2 Daughters and mother</td>
<td>39</td>
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<td>Headache</td>
<td>440</td>
<td>NR</td>
<td>Optic disc pallor</td>
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<tr>
<td></td>
<td></td>
<td>30</td>
<td>Obese</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>Obese</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>—</td>
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</table>

(Continued on next page)
<table>
<thead>
<tr>
<th>Family</th>
<th>Relationships of Family Members with IIH</th>
<th>Age at Diagnosis (years)</th>
<th>Habitus (BMI†)</th>
<th>Presenting Symptom</th>
<th>Lumbar Puncture Opening Pressure (mm water)</th>
<th>Brain MRI/CT Findings</th>
<th>Papilledema description or Frisen Grade</th>
<th>Associated Features</th>
</tr>
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<tbody>
<tr>
<td>7</td>
<td>Daughter and mother</td>
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<td>Obese (34)</td>
<td>Headache</td>
<td>240, 320</td>
<td>Empty sella</td>
<td>I</td>
<td>Tetracycline use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>Obese</td>
<td>Headache</td>
<td>NR</td>
<td>Empty sella</td>
<td>NR</td>
<td>Now has chronic headache</td>
</tr>
<tr>
<td>8</td>
<td>Second cousins (male)</td>
<td>25</td>
<td>Muscular (35)</td>
<td>Transient visual obscuration</td>
<td>400</td>
<td>Normal</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Second cousin (female)</td>
<td>30</td>
<td>Thin</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>III</td>
<td>Sister with chronic HA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51</td>
<td>Obese (43)</td>
<td>Headache</td>
<td>NR</td>
<td>Normal</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Mother and daughter</td>
<td>38</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>BL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
<td>Obese</td>
<td>Headache</td>
<td>NR</td>
<td>NR</td>
<td>BL</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Mother and daughter</td>
<td>61</td>
<td>Obese (50)</td>
<td>Headache</td>
<td>290</td>
<td>Empty sella</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>Obese (36)</td>
<td>Headache</td>
<td>270</td>
<td>Empty sella</td>
<td>0</td>
<td>Chronic headache</td>
</tr>
</tbody>
</table>

BMI, body mass index; NR, not recorded; IIH, idiopathic intracranial hypertension.
FIG. 1. Optic disc photographs of Family 1. A. Index case (daughter, 25 years old). Papilledema grade I; lumbar puncture (LP) opening pressure (OP) 420 mm water. B. Mother, 47 years old. Papilledema grade II; OP 220 mm water. C. Daughter, 16 years old. Papilledema grade I; OP 270 mm water. D. Daughter, 18 years old. Papilledema grade I; OP 220 mm water. E. Daughter, 13 years old. Papilledema grade I; OP 290 mm water.

Family 8:
Second Cousins

The index case was a 25-year-old muscular man who presented with TVO. He had a BMI of 31 kg/m² and grade III papilledema. His OP was 400 mm water, and he had been treated with acetazolamide. He mentioned that his second cousin, who lived in Hawaii, also had the diagnosis of “pseudotumor cerebri.” The patient reported that his cousin was “thinly built.”

Family 9:
Second Cousins

The index case was a 51-year-old woman with headache and TVO. She was extremely obese (BMI 43 kg/m²) and had grade III papilledema. OP was 450 mm water. She reported that her second cousin also had a diagnosis of IIH and was being treated. No medical records of her cousin’s diagnosis were obtainable.

Family 10:
Mother and Daughter

The index case was a 38-year-old woman in whom IIH was diagnosed on the basis of grade III papilledema and an OP of 410 mm water. She had chronic daily headache. She mentioned that her deceased mother had once had a diagnosis of pseudotumor cerebri and had been treated by a neuro-ophthalmologist in Boston. We were unable to obtain medical records.

Family 11:
Mother and Daughter

The index case was the 52-year-old mother who had chronic headache and unilateral papilledema. She was extremely obese (BMI 50 kg/m²). OP was 290 mm water, and she was treated with acetazolamide. Her daughter accompanied her during the visit and reported that she, too, had chronic headache. She was obese (BMI 36 kg/m²) and had an OP of 270 mm water but no papilledema. After LP, she developed radicular pain in both legs and the right arm. Both patients had a radiographically empty sella turcica.

SUMMARY OF CASE MATERIAL

Of the 11 families in our cohort, we identified 25 women and 2 men. Fourteen patients had definite IIH and 13 had probable IIH. Of the 23 family members for whom we could obtain body habitus details, 21 were obese. Of 21 patients for whom CSF OP was available, 14 had OP greater than 250 mm water, 2 had OP less than 250 mm water, 4 had unconfirmed reports of “high OP,” and 1 had a dry tap. Among the 19 patients for whom imaging results
<table>
<thead>
<tr>
<th>Study</th>
<th>Relationships of Family Members with IIH</th>
<th>Age at Lumbar Puncture (years)</th>
<th>Habitus (BMI*)</th>
<th>Lumbar Puncture Opening Pressure (mm water)</th>
<th>Imaging</th>
<th>Papilledema description or Frisen Grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buchheit, 1969 (9)</td>
<td>Sisters</td>
<td>19</td>
<td>Obese</td>
<td>270</td>
<td>X-ray, angiogram and pneumoencephalogram normal</td>
<td>3 diopters</td>
<td>Two other sisters normal</td>
</tr>
<tr>
<td>Siegel et al, 1972 (4)</td>
<td>Sister and brother</td>
<td>24</td>
<td>Not obese</td>
<td>400</td>
<td>Widening of cranial sutures on x-ray</td>
<td>3 diopters</td>
<td>Normal optic disc</td>
</tr>
<tr>
<td>Venable, 1973 (21)</td>
<td>Mother and daughter</td>
<td>2.5</td>
<td>Not obese</td>
<td>‘Elevated’</td>
<td>X-ray, angiogram and pneumoencephalogram normal</td>
<td>3 diopters</td>
<td>Vitamin A intoxication</td>
</tr>
<tr>
<td>Howe et al, 1973 (7)</td>
<td>Sisters</td>
<td>27</td>
<td>Obese</td>
<td>NR</td>
<td>Air ventriculogram: ‘bulging brain’</td>
<td>‘Bilateral papilledema leading to optic disc pallor’</td>
<td>IIH diagnosis by historical records (history of multiple LPs and burr holes to relieve symptoms)</td>
</tr>
<tr>
<td>Rothner et al, 1974 (15)</td>
<td>Mother and son</td>
<td>38</td>
<td>Obese</td>
<td>280–430</td>
<td>X-ray, Hg197 brain scan normal</td>
<td>No grade</td>
<td>4 weeks postpartum</td>
</tr>
<tr>
<td>Mikkelsen et al, 1974 (5)</td>
<td>Homozygous twin brothers</td>
<td>12</td>
<td>Obese</td>
<td>200–300</td>
<td>No grade</td>
<td>No grade</td>
<td>Vitamin A for psoriasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>Not obese</td>
<td>160–200</td>
<td>X-ray, ventriculography normal</td>
<td>1–2 diopters</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>Not obese</td>
<td>NR</td>
<td>X-ray normal</td>
<td>1 diopters</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Relationships of Family Members with IIH</td>
<td>Age at diagnosis (years)</td>
<td>Habitus (BMI*)</td>
<td>Lumbar Puncture Opening pressure (mm water)</td>
<td>X-ray: mild enlargement of sella turcica; brain scan, pneumoencephalogram and arteriogram normal</td>
<td>Papilledema description or Frisen Grade</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------------</td>
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<td>----------------------------------------------------------------------------------------</td>
<td>----------------------------------------</td>
<td>----------</td>
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<td>Traviesa et al, 1976 (20)</td>
<td>Sisters</td>
<td>41</td>
<td>Obese</td>
<td>530</td>
<td>X-ray, brain scan, echoencephalogram normal</td>
<td>No grade</td>
<td>4 months pregnant</td>
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<tr>
<td></td>
<td></td>
<td>22</td>
<td>Obese</td>
<td>540</td>
<td>X-ray, brain scan, echoencephalogram normal</td>
<td>No grade</td>
<td></td>
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<tr>
<td>Shapiro et al, 1980 (18)</td>
<td>Mother and daughter</td>
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<td>Obese</td>
<td>280</td>
<td>Empty sella</td>
<td>No grade</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>Obese</td>
<td>550</td>
<td>Angiography, ventriculography, pneumoencephalography normal</td>
<td>2–3 diopters</td>
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<tr>
<td>Coffey et al, 1982 (10)</td>
<td>Sisters</td>
<td>19</td>
<td>Not obese</td>
<td>580</td>
<td>CT normal</td>
<td>No grade</td>
<td>Major depressive episode in both sisters, 12 and 8 months before IIH symptoms</td>
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<tr>
<td>Torlai et al, 1989 (19)</td>
<td>Heterozygous twin brothers</td>
<td>27</td>
<td>Not obese</td>
<td>420</td>
<td>CT normal</td>
<td>No grade</td>
<td>Presented within 3 months although living in separate geographical locations; clinical picture similar to bilateral choroidal folds and similar clinical course</td>
</tr>
<tr>
<td></td>
<td></td>
<td>58</td>
<td>NR</td>
<td>450</td>
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<td>No grade</td>
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<td>CT normal</td>
<td>No grade</td>
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<thead>
<tr>
<th>Study</th>
<th>Relationships of Family Members with IIH</th>
<th>Age at Lumbar Puncture (years)</th>
<th>Habitus (BMI*)</th>
<th>Lumbar Puncture Opening pressure (mm water)</th>
<th>Imaging</th>
<th>Papilledema description or Frisen Grade</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Johnston et al, 1991 (11)</td>
<td>Mother, 2 daughters and 1 son</td>
<td>33</td>
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<td>&quot;Elevated&quot;</td>
<td>CT normal</td>
<td>No grade</td>
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<td>22</td>
<td>Obese</td>
<td>NR</td>
<td>CT normal</td>
<td>No grade</td>
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<td>25</td>
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<td>NR</td>
<td>CT normal</td>
<td>No grade</td>
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<td>17</td>
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<td>&quot;Elevated&quot;</td>
<td>Enlarged ventricles with communicating hydrocephalus</td>
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<td>Kharode et al, 1992 (13)</td>
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<td>465</td>
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<td>&quot;Mild&quot;</td>
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<td>Rogel Ortiz et al, 1994 (14)</td>
<td>Father and daughter</td>
<td>16</td>
<td>Obese (34)</td>
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<td>43</td>
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<td>9</td>
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<td>355</td>
<td>CT head, MRI and arteriogram normal</td>
<td>No grade</td>
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<td>Gardner et al, 1995 (6)</td>
<td>Heterozygous twin sisters</td>
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<td>460</td>
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<td></td>
<td></td>
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<td>NR</td>
<td>MRI not done</td>
<td>No grade</td>
<td>CSF rhinorrhea; virtually identical clinical course; nearly simultaneous onset of symptoms in both twins at 12 years; diagnosed with papilledema at 19 years; sister 1 had CSF rhinorrhea at 21 years</td>
</tr>
<tr>
<td>Fujiwara et al, 1997 (8)</td>
<td>Homozygous twin sisters</td>
<td>19</td>
<td>Not obese</td>
<td>340</td>
<td>Enlarged ventricles, empty sella in both on MRI</td>
<td>Bilateral papilledema leading to optic disc pallor within 3 years</td>
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<td></td>
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<td>Imaging</td>
<td>Papilledema description or Frisen Grade</td>
<td>Comments</td>
</tr>
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<td>-----------------------------------------------------------------------------------------------</td>
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<tr>
<td>Salmaggi et al, 1996 (16)</td>
<td>Father and daughter</td>
<td>51</td>
<td>NR</td>
<td>NR</td>
<td>Empty sella on CT</td>
<td>No grade</td>
<td>Another daughter had similar visual symptoms but not examined</td>
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<td></td>
<td></td>
<td>18</td>
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<td>700</td>
<td>Empty sella on CT</td>
<td>Optic disc pallor</td>
<td>Recurrences after pregnancy twice (22 years, 26 years)</td>
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<tr>
<td>Santinelli et al, 1998 (17)</td>
<td>Mother and 2 sons</td>
<td>36</td>
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<td>400</td>
<td>MRI normal</td>
<td>No grade</td>
<td>Hyperreflexia with spinal and radicular pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>Not obese</td>
<td>350</td>
<td>MRI normal</td>
<td>No grade</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td>Not obese</td>
<td>400</td>
<td>MRI normal</td>
<td>No grade</td>
<td></td>
</tr>
<tr>
<td>Karaman et al, 2003 (12)</td>
<td>Mother, 2 daughters and 3 cousins</td>
<td>54</td>
<td>Not obese</td>
<td>450</td>
<td>Empty sella on MRI</td>
<td>5</td>
<td>Grandmother died 34 years earlier; had symptoms similar to those of the other family members; 15 family members examined in all</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36</td>
<td>Obese</td>
<td>Refused LP</td>
<td>Empty sella on MRI</td>
<td>1–2</td>
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</tr>
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<td>Obese</td>
<td>500</td>
<td>Empty sella on MRI</td>
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<td>Obese</td>
<td>Refused LP</td>
<td>MRI normal</td>
<td>1–2</td>
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<td>17</td>
<td>NR</td>
<td>Refused LP</td>
<td>Empty sella on MRI</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>Not obese</td>
<td>Refused LP</td>
<td>MRI normal</td>
<td>1–2</td>
<td></td>
</tr>
</tbody>
</table>

NR, not recorded; LP, lumbar puncture; IIH, idiopathic intracranial hypertension; NLP, no light perception; CSF, cerebrospinal fluid.

*Where available.
were available, 8 had an empty sella, 2 had a Chiari I malformation, and, 9 had reportedly normal studies. Four patients from 2 families had psychiatric illness.

**DISCUSSION**

Considering that without any systematic effort to screen family members of patients with IIH, we incidentally discovered 11 families of IIH in our cohort of 237 cases, the paucity of reported familial cases of IIH seems surprising (Table 2). We rejected 2 reports as unquestionable examples of vitamin A intoxication (4,5). Another study reported IIH subsequent to tetracycline ingestion (6), and two others reported radiographically enlarged ventricles (7,8).

After we excluded these 5 reports, we found 13 reported families of IIH comprising 33 individuals (25 women and 8 men) (9–21). There are, however, limitations to most of these reports. Depending on the medical source of the case report, the information regarding the ophthalmic, neurologic, and general physical examinations and the details of the LP and imaging varied considerably. At least 7 of these case reports antedated computed tomography. In those reports, information was based on ventriculography or pneumoencephalography.

Despite these limitations, the earlier reports offer valuable insights. Nine of the 13 reports describe parent-child combinations and four describe sibling combinations (Table 2). These findings are remarkably similar to ours, in which 7 of 11 families had parent-child combinations and four had sibling-sibling combinations.

Our findings, together with those reported previously, strongly suggest a dominant inheritance, although the genetics of familial IIH are far from clear. In our series, the age of onset of symptoms was remarkably similar for the index case and the other affected family member or members. This trend was also seen in at least 6 of the families reported previously. Traviesa et al (20) reported non-twin siblings who had the onset of symptoms at a similar age although the symptoms were separated in time. Torlai et al (19) reported heterozygous twin brothers who developed symptoms of IIH within a few months even though they were living in separate cities. Venable (21) reported that the age of onset of IIH was similar in mother and daughter. These case reports hint at a genetic “clock” involved in the pathogenesis of familial IIH.

Johnston et al (11) reported a family that included a mother and 5 children (4 daughters and 1 son) who were examined for IIH. The mother, 3 daughters, and son had developed papilledema with elevated ICPs, although exact pressure measurements were not documented. Although the son did not meet the modified Dandy criteria, as he had communicating hydrocephalus, all other family members did. The authors hypothesized that communicating hydrocephalus and IIH are likely to be caused by a pathogenetic mechanism responsible for a continuum of disorders of CSF circulation owing to malabsorption of CSF at the arachnoid villi. Thus, the occurrence of hydrocephalus and IIH in the same family appeared to them to be more than a coincidence.

The largest extended family report comes from Croatia (12) where 15 members of a family were screened and 7 with possible IIH were identified. Six of 15 members examined had varying Frisen grades of papilledema. The deceased grandmother’s old hospital records indicated she had symptoms of IIH. CSF OP was elevated in the 2 family members who agreed to undergo a LP, but other family members refused. An empty sella was seen in 4 members of the family.

The largest family in our series consisted of 5 members, a mother and all 4 of her daughters (Family 1). All were obese and 4 were extremely obese. OP was elevated in 3 family members and borderline in 2. They all had chronic migraine-like headache. Papilledema was mild (Frisen grade I or II) in all 5 women, and visual acuity, visual field, and color vision were normal in all.

Two families in our cohort had a DSM IV psychiatric condition. Manic psychosis was seen in one sibling and a major depressive disorder was seen in the second sibling in the family of heterozygous twins. Bipolar disorder was diagnosed in another set of siblings whose mother also had a major depressive disorder. Coffey et al (10) described 2 sisters who developed IIH within 2 weeks of resolution of major depression. They hypothesized that the development of IIH is probably related to “a state of endogenous steroid withdrawal following the normalization of a steroidal abnormality that accompanies depression.” Other authors (24) have also noted an association between IIH and depression.

As in previous reports, our case series has all the limitations of any retrospective series. There was no systematic effort to identify familial cases in all 237 patients of our cohort. Thus, our numbers may substantially underestimate the incidence of familial IIH. In a number of our patients, the family history was obtained from the index patient with no corroborating information from the primary source despite our best efforts. This was especially true when the occurrences of IIH were separated widely in time or the affected family members were dispersed geographically. Furthermore, not all family members had documented LP and/or OP. Patients were often referred for second or third opinions and had previously undergone evaluation at other facilities, where LP had often been performed by radiologists, internists, or emergency physicians and OP had not been recorded. In such cases, we were forced to rely on the patients’ history, repeating what they were told during the procedure regarding elevated OP or on their reports of improvement of symptoms after LP. The problem of the lack of OP measurements is compounded when the BMI is markedly elevated and a successful LP frequently requires the use of longer needles and must be done under fluoroscopy. Under those circumstances, the LP is often performed with
the patient in the prone position. It is not yet known whether
the OPs obtained when the patient is lying in the lateral
decubitus and prone positions are comparable.

There are a number of reasons for under-recognition of
familial IIH. The clinical presentation of patients with IIH is
varied. Patients with IIH, headache, and papilledema are
easily identified. However, IIH in patients without papil-
dedema or in patients with papilledema and no headache is
often not correctly diagnosed. Of the patients in our original
cohort of 237, 7.5% had no papilledema, including at least 2
of the reported family members (Families 4 and 11). Some
11% of the patients were asymptomatic and IIH was only
diagnosed when papilledema was incidentally found during
a routine eye examination for glasses. Family members may
have been symptomatic with papilledema in the past but may
now demonstrate only residual signs of earlier optic disc
swelling and raised ICP. Unless physicians are looking for
these signs, affected family members may remain un-
recognized. Occasionally family members recalled being
told of a radiographically empty sella turcica, often construed
as a sign of chronically raised ICP. Confirmation of raised
ICP in this circumstance is often difficult, as potentially
affected family members see no reason to undergo a LP.

Another practical problem in investigating familial
IIH is that families are frequently separated geographically,
and it is logistically difficult to personally examine each
family member. Finally, examination of a patient at a single
point may not be truly representative of the spectrum within
which IIH is seen. CSF pressure is variable from hour to
hour. In a patient with signs and symptoms of IIH, a single
normal OP does not eliminate the diagnosis. Some patients
with IIH continue to have raised ICP on LP performed
several years after the initial diagnosis despite resolution of
papilledema (25). If the signs and symptoms of IIH have
resolved, the only definitive test is LP, although the offer of
LP is very easy to turn down when one is asymptomatic.

The current case series of familial IIH identified in
a single institution essentially doubles the number of
previously reported cases. First-degree relatives of patients
with IIH should be routinely screened for signs and
symptoms of IIH and when appropriate, offered LP and
brain MRI. A systematic analysis of families with IIH may
yield useful information about the pathogenesis of a condition
that still remains idiopathic more than 100 years after the first report by Quincke (26).

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More than 6,000 abstracts were presented at the annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), Fort Lauderdale, FL, April 27–May 1, 2008. Available at www.arvo.org, the abstracts are referenced by program number.

This year the focus was “Eyes on Innovation.” The keynote address was given by Ray Kurzweil, a leader in groundbreaking technologies such as the CCD flat-bed scanner, omni-font optical character recognition, the print-to-speech reading machine for the blind, and the text-to-speech synthesizer.

The Proctor Medal was awarded to Robert Miller, MD, University of Minnesota, for his work on cell communication mechanisms in the vertebrate retina. Dr. Miller has made seminal discoveries on the basic mechanisms through which nerve cells of the retina communicate. He identified inhibition in the retina, paving the way for new knowledge on the processes of excitation and neurotransmission mediated by peptides. The Weisenfeld Award went to George Waring III, MD, a leader in the field of refractive surgery, who spoke about refractive surgery, visual impairment, and quality of life. The Friedenwald Award winner was Lois Smith, MD, PhD, whose research is directed at understanding the causes of retinopathy of prematurity and on developing methods to prevent it. Dr. Smith has made seminal contributions in promoting understanding of vascular endothelial and insulin-like growth factors in pathologic retinal angiogenesis.

**NEUROPROTECTION**

Virus-mediated gene delivery of the normal human complex I subunit ND4, mutations of which are responsible for many forms of Leber hereditary optic neuropathy (LHON), reduced retinal ganglion cell degeneration in a rodent model of LHON (#3239). The gene inserts into the chromosomal DNA and contains a mitochondrial targeting sequence to subsequently direct the normal ND4 to the mitochondria. Initial clinical trials of this therapy in LHON have been approved.

Allotypic expression of a mutant human ND4 subunit of mitochondrial complex I recapitulates the hallmarks of LHON in the mouse, as demonstrated by an induction of optic nerve swelling and apoptosis with a progressive demise of ganglion cells. Superoxide dismutase 2 gene transfer protected against optic neuropathy induced by mutant human ND4 by suppressing reactive oxygen species and providing long-term protection against ganglion cell loss in the retina and axonal loss in the optic nerve (#4359). The study suggests that this form of gene therapy may be useful after the onset of disease in LHON at a time when allotypic normal ND4 was not able to rescue mitochondrial function.

SIRT1 belongs to the family of type III histone deacetylases and is implicated in diverse cellular processes. Nicotinamide adenine dinucleotide (NAD)+-dependent protein deacetylase SIRT1 regulates cellular apoptosis. Oral administration of SIRT1-activating compounds attenuated neurodegeneration in a mouse model of multiple sclerosis (#3240). The drug penetrates the eye and prevents retinal ganglion cell loss during acute optic neuritis. It also reduces neurologic dysfunction from spinal cord axonal damage during disease remission.

Injection of granulocyte-macrophage colony-stimulating factor (GM-CSF) into the third brain ventricle significantly attenuated retinal ganglion cell loss in a rat model of ischemic optic neuropathy (#3242). Neuroprotection was conferred with treatment 3 days after ischemic injury and appears to be mediated by increased recruitment of extrinsic macrophages into the optic nerve.

Conditions that allow regeneration of retinal ganglion cell axons after traumatic injury were reported (#3243). Blocking the NOGO receptor, which binds myelin-derived axonal growth inhibitors, allowed sprouting of new axons posterior to the injury site in mutant mice containing increased expression of bcl-2, which promotes axonal growth, and lacking the glial fibrillary acidic protein and vimentin genes required for glial scarring. Results suggest that combining promotion of axonal growth with blocking of growth inhibitors and scarring promoters permits axonal regeneration.

Matrix metalloproteinase-7 (MMP-7) and vascular endothelial growth factor may have important roles in maintaining axonal structure after injury. Optic nerve bundles in MMP-7 knockout mice had irregular shape, organization, and myelination, and traumatic nerve injury.
resulted in decreased MMP-7 expression and increased VEGF expression (#4356).

NAD may have neuroprotective effects in toxic or inflammatory optic neuropathies. Tumor necrosis factor injection into rodent eyes induced axonal loss, with decreased levels of NAD. Exogenous NAD was able to reduce axonal loss through suppressed activation of microglia (#4358).

The role of the melanopsin pupillary light reflex in patients with retinal photoreceptor disease was studied by using Ganzfeld red and blue stimuli (#3245). The authors were able to demonstrate that patients with rod or cone degeneration had diminished pupil response to red or dim blue light but intact pupillary constriction to bright blue light, which may aid in localization of disease.

OPTIC NERVE

Peripapillary nerve fiber layer (ppNFL) thickness was measured using Fourier domain optical coherence tomography (FD-OCT) in 39 control subjects and 22 patients with nonarteritic anterior ischemic optic neuropathy (NAION) (#936). The superior and inferior hemisphere average of the automated visual field total deviation and pattern deviation were compared with superior and inferior hemisphere average of the ppNFL thickness. The NAION group had a significantly thinner ppNFL in every quadrant and octant compared with that in the normal group. The relative loss was greatest in the superior quadrant and superior-temporal octant. The most severe hemispheric visual field loss was associated with a residual ppNFL thickness of 32 m. FD-OCT was able to measure ppNFL thickness with excellent reproducibility both in normal subjects and in patients with NAION. Severity and location of visual field defects were significantly correlated with ppNFL thinning.

The ability of optical coherence tomography (OCT), GDx, and Heidelberg retinal tomography (HRTIII) to detect permanent optic nerve damage was assessed in patients with a history of acute unilateral retrobulbar optic neuritis (#820). The study included 25 patients and 29 control subjects. Both OCT and GDx were good for differentiating optic neuritis and control eyes with a high level of sensitivity and specificity, whereas HRTIII cannot make such a differentiation. There was good correlation between standard visual function tests and retinal nerve fiber layer (RNFL) imaging and visual evoked potential P-100 amplitude.

OCT and GDx were used to study the RNFL of 40 patients evaluated within 21 days of onset of vision loss in a first episode of typical acute optic neuritis (#5389). Swelling or thickening of the RNFL was defined as 3 sectors of $10\%$ thickness compared with the unaffected fellow eye. More than 85% of patients had RNFL swelling by OCT measurement. RNFL loss could be observed within 1 month of onset of optic neuritis. There was no correlation between RNFL thickness and the retrobulbar distance of the demyelinating lesion from the globe. The investigators concluded that when demyelinating lesions are distal to the globe, axoplasmic blockade at the site of the lesion and not inflammation of the optic disc region could be the cause of RNFL swelling.

Optic nerve axonal loss was studied prospectively with OCT in 93 consecutive patients with multiple sclerosis (MS) and normal subjects (#1181). The group with MS included 47 patients who had had optic neuritis and 46 who had not. Among the patients with MS, 60 had the relapsing remitting form, 8 had the primary progressive form, and 25 had the secondary progressive form. No significant relationship was found between RNFL thickness and Expanded Disability Status Scale (EDSS) score or MS type. The average RNFL thickness for the whole MS patient group was 90 m compared with 104 m for the healthy group. Average RNFL thickness for patients with MS without previous optic neuritis was 94 m. The investigators concluded that there were highly significant reductions in RNFL thickness in affected eyes of patients (with or without previous acute optic neuritis) compared with control eyes. RNFL thickness as measured by OCT was found to correlate with the level of relative afferent papillary defect measured with neutral density filters (#1182). Frequency domain OCT was used to measure the relative contribution of blood vessels to overall RNFL thickness (#1184). Blood vessels comprised a mean of 7% of RNFL thickness in normal eyes and 12% in areas of major arcuate fiber bundles. In eyes with severe visual field loss, blood vessels comprised a mean of 24% in areas of major arcuate fiber bundles.

OCT thickness of RNFL correlated with clinical grading of optic disc edema, but thickening of only the inferior portion of the optic disc correlated with Humphrey visual field (HVF) mean deviation (#1185).

A study of patients with idiopathic intracranial hypertension (IIH) showed no consistent correlation between RNFL thickness on OCT and visual field loss on HVF, noting that a combination of atrophy and swelling can coexist (#1186). A smaller study did show that improvement in OCT-measured RNFL thickness after acute papilledema in IIH correlated with improvement in HVF mean deviation (#1187). Optic disc area measured by Heidelberg retinal tomography (#1189) demonstrated that Caucasians have smaller discs ($2.15 \pm 0.55 \text{ mm}^2$) than African Americans ($2.55 \pm 0.51$), Asian Americans ($2.38 \pm 0.54$), Filipino Americans ($2.48 \pm 0.70$), and Hispanic Americans ($2.57 \pm 0.55$).

Matrix frequency doubling technology (FDT) 30-2 visual field defects correlated with standard HVF field 30-2 fields in at least 3 quadrants of 71% of patients with a variety of neuro-ophthalmic causes for vision loss (#1192), including cortical, chiasmal, and optic nerve disease.
Average visual field loss in FDT testing as a measure of contrast sensitivity could discriminate patients with Alzheimer disease (AD) from healthy control subjects and patients with mild cognitive impairment (#1194).

FDT matrix visual field testing was more sensitive than earlier versions of FDT and paralleled HVF 24-2 Swedish Interactive Thresholding Algorithm (SITA) Fast testing for detecting visual field loss respecting the vertical midline (#1196).

Anterior optic nerve cross-sectional area measured on MRI did not correlate with visual acuity or color vision loss, but did correlate with HVF mean deviation in patients with optic atrophy (#1197).

A series of 20 patients undergoing evaluation and treatment of pituitary tumors were subjected prospectively to standard automated perimetry (SAP) (24-2 SITA Fast) and Rarebit visual field testing (#1195). The pattern of visual field defects seen on SAP was duplicated by Rarebit in all cases. In 4 patients with normal SAP after pituitary treatment, persistent visual field defects could still be seen in the Rarebit, indicating subclinical pathologic changes. The use of tiny suprathreshold stimuli may be a sensitive way of looking for residual defects seen in patients with chiasmal syndromes.

In a retrospective interventional clinical case study, the records of 7 patients (8 eyes) were reviewed to study the functional and anatomic outcomes of triamcinolone acetonide intravitreal injection for NAION (#6008). Visual acuity improved in 6 (85%) patients with a mean improvement of 3.5 lines. Two patients (25%) had loss of visual acuity with a mean worsening of 4 lines. Among 6 patients with improved acuity, visual field mean deviation improved slightly in one patient (12.5%) and showed no significant overall change in 5 patients (62.5%). The benefit of intravitreal steroid use in NAION could not be clearly demonstrated in this small study.

In an ultrastructural study of induced optic neuropathy in a mouse model (#4362), chloramphenicol administered orally in high doses for 15 days resulted in axonal condensation and nerve fiber degeneration, remyelination, neuronal reactivity, and cell death. Gliotic changes were the most pronounced morphologic evidence for cell injury as observed by astrocytic hypertrophy and hyperplasia, oligodendrocytic remyelination of demyelinated axons, and apoptotic changes. The increase in the number of mitochondria may be a compensatory reaction to impairment in oxidative phosphorylation induced by chloramphenicol.

An ultrastructural study of the optic nerve was carried out in a mouse model for conditional knockout gene mitofusin 2 (Mfn2) (#5383) associated with mitochondrial fusion, a phenomenon that occurs with remodeling in the cell. Impairment of fusion causes mitochondrial fragmentation. Mouse models of Mfn2 that cause conditional knockout only in the visual system have been developed. This study revealed that axonal profiles of knockout mice show degenerative changes, condensation of axoplasm and mitochondria, an increased number of microglia, a decrease in oligodendrocytes, and the appearance of astrocytes with giant mitochondria. This model may serve as a tool to observe how mitofusins contribute to optic atrophy and to other neurologic disorders associated with aberrant mitochondrial fusion.

Retinal ganglion cells were simultaneously identified and levels of reactive oxygen species were measured in vivo using a dual frequency confocal scanning laser ophthalmoscope (#5384). This information is helpful in studying the mechanisms of apoptosis that occur with retinal ganglion cell injury.

Previous histologic studies have shown optic nerve axonal degeneration in AD. The receptor for advanced glycation end-products (RAGE) is a possible mediator in the pathogenesis of many neurodegenerative diseases. RAGE can play a role in the signal transduction pathways leading to amplification and perpetuation of inflammation. Ten optic nerves from patients who died of AD were examined immunohistochemically (#5385). An increase in RAGE was found in optic nerves in patients with AD compared with those of control subjects. RAGE expression was associated with glial cells in AD optic nerves compared with control nerves. A linear relationship of RAGE expression with age was found in AD optic nerves with increased RAGE expression in AD optic nerve axons and glial cells. RAGE up-regulation in AD is a possible compensatory phenomenon or cellular adaptation. It is not known whether this up-regulation is a cause or consequence of AD.

Brain metabolic changes in cortical gray and normal-appearing white matter (NAWM) were studied with 1H magnetic resonance spectroscopy to determine the prognostic value of metabolic alterations in patients with clinically isolated syndromes (CIS) suggestive of MS and presenting as optic neuritis (#613). Using a 3-T whole body magnetic resonance system, a multisquence conventional MRI protocol, and single voxel proton magnetic resonance spectroscopy of the parietal NAWM, studies were performed in 30 patients presenting with optic neuritis at baseline and 20 control subjects. The metabolic concentrations of N-acetylaspartate (NAA), myo-inositol (M3), choline, and creatine were determined at baseline and at 6, 12, 18, and 24 months after the initial demyelinating event. In this study, 11 patients converted to definite MS during the follow-up period. The patients who converted to MS showed significantly lower baseline NAA concentrations (P < 0.01) and higher INS concentrations (P < 0.01) in the NAWM compared with those in nonconverters. No significant difference was observed for creatine and choline in either patient group. No significant differences were observed...
between any metabolite concentrations from the non-converted group and control group. The early increase in INS and decrease in NAA may reflect a process of pathogenic importance in MS NAWM. NAA and INS brain concentrations may be a prognostic marker for conversion to early definite MS.

**EYE MOVEMENTS**

Mechanically restricting microsaccades, present during normal fixation, with a scleral contact lens (#129) also leads to microsaccade suppression in the contralateral eye. The authors suggested that proprioceptive inputs play a role in suppressing microsaccades in dark conditions.

Examination of prediagnosis carriers of the Huntington gene showed a significant decrease in visual scanning measurements up to 5–6 years before clinical diagnosis of Huntington disease (#131) that may be useful as a biomarker of early disease.

Involuntary version-vergence nystagmus induced by motion stimuli demonstrated that although the vergence and saccadic systems can act separately, they interact, with vergence velocity dependent on saccadic velocity, when both systems are stimulated simultaneously (#134).

Investigators looked at primates with prism-induced strabismus as a surrogate for amblyopia in infantile esotropia in assessing the potential benefit of early intervention. They found that binocular connections between the ocular dominance columns are diminished if primates are subjected to prism-induced strabismus and that sensory and ocular motor defects can be prevented if correction occurs between 3 and 12 weeks (corresponding to 3 and 12 human months). This finding suggests that early intervention in humans may be beneficial for appropriate brain development.

Five adult patients who underwent tenotomy for infantile nystagmus had improved target acquisition times, correlating with subjective improvement in vision (#137).

MRI demonstrated abnormalities in 47 of 48 patients with infantile nystagmus (#138), ranging from signal abnormalities in the white matter (44%), gray matter (42%), and brainstem (44%), to specific cranial anomalies (38%), developmental malformations (35%), cerebral atrophy (17%), and enlarged subarachnoid and Virchow-Robin spaces (35%).

Soft contact lenses were found to dampen the slow phases of infantile nystagmus (#140), possibly by feedback signaling through the fifth cranial nerve, resulting in a wider range and degree of foveation.

Mechanical restriction of eye movements with a handle-held scleral contact lens in one eye of patients with infantile nystagmus resulted in reduced amplitude of nystagmus in both eyes (#141) and may be useful for times when nystagmus needs to be dampened during clinical evaluation.

**ORBIT**

Progressive enophthalmos to a degree that the globes lose contact with the eyelids can occur after cerebrospinal fluid (CSF) shunting for acquired hydrocephalus. Based on volumetric image analysis, the results of one study of 4 patients (#6022) suggested that enophthalmos after CSF shunting is secondary to expansion of bony orbital volume that may be due to chronic CSF hypotension. Possible mechanisms for enophthalmos include fat atrophy or tethering of the globes via tension on the optic nerves due to a posterior shift in the position of the brain.

A symposium on thyroid-related orbitopathy (TRO) focused on attempts to translate basic science discoveries into clinical therapy including core components of pathophysiology and valid scales in assessing clinical disease. Orbital fibroblasts may possess unique properties that separate them from other fibroblasts with special roles for insulin-like growth factor (IGF-1) receptor and thyroid-stimulating hormone (TSH) receptor in accelerating fibroblast proliferation and inflammation. The IGF-1 receptor has been identified in patients with TRO but in few patients without disease. This receptor may be overexpressed in orbital tissue; binding of antibody to receptor may lead to altered cell function. The TSH receptor is not always expressed except in specific conditions. Is there a link between TSH and IGF-1 receptors in the orbit? Evidence of their close physical linkage was reviewed along with data suggesting that the receptors may interact with each other. Such interaction suggests the possibility that an initiating event leads to autoantibodies generated against epitopes in the TSH and IGF-1 receptors. Spread could occur so that autoantigens are incorporated in a step-like fashion, leading to generation of cytokines and chemotactants. There could be overexpression of extracellular matrix and hyaluronic acid until clinical disease is manifested. Although there have been prior classification systems of TRO, such as ‘‘NOSPECS,’’ a newer algorithm called ‘‘vision, inflammation, strabismus, appearance/exposure’’ (VISA) was proposed.

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The 60th Annual Meeting of the American Academy of Neurology took place in Chicago, Illinois, from April 12 to 19, 2008. Eleven educational courses in the field of neuro-ophthalmology and neuro-otology were given, ranging from breakfast seminars to the traditional all-day course. Faculty included Robert Baloh, MD, Valerie Biousse, MD, James Corbett, MD, Wayne Cornblath, MD, Kathleen Digre, MD, Eric Eggenberger DO, Scott Eggers, MD, Terry Fife, MD, Steven Galetta, MD, Timothy Hain MD, Janet Helminski, PhD, Aki Kawasaki, MD, R. John Leigh, MD, Mark Moster, MD, Nancy Newman, MD, Valerie Purvin, MD, Janet Rucker, MD, Barbara Scherokman, MD, Jade Schiffman, MD, Michael Strupp, MD, Rosa Tang, MD, Jonathan Trobe, MD, Ronald Tusa, MD, Michael Wall, MD, and David Zee, MD.

Approximately 1,560 scientific platform papers and posters were presented at the meeting. The material of most interest to neuro-ophthalmologists is summarized here.

**NEURODEGENERATIVE DISEASES**

A flash electroretinogram (ERG) study of 16 patients with dementia with Lewy bodies (DLB) demonstrated photopic a-wave and photopic and scotopic b-wave abnormalities. Pathologic analysis in 6 retinas showed cytoskeletal disorganization of the cone photoreceptor layer, pale inclusions in the outer plexiform layer and abnormal distribution of synucleins. No similar findings were seen in patients with Parkinson disease (PD) with visual hallucinations or in normal control retinas. DLB appears to differ from PD in the higher frequency of visual hallucinations, which may be of retinal origin, given the structural abnormalities discovered in the inner retina in DLB (Devos D, Lille, France, P01.188).

The Useful Field of View (UFOV) test has been predictive of the ability to perform activities of daily living, including driving. Patients with PD and age-matched control subjects referred to a driving rehabilitation specialist underwent the UFOV test, which was correlated with driving outcomes. Patients with PD performed significantly worse than the control group in UFOV subtests 1 (visual processing speed) and 2 (divided attention). Lane maintenance errors and rating of crash risk were significantly and strongly correlated with UFOV subtests 1 and 2 (McCarthy DP, Gainesville, FL, P01.192).

Abnormalities in contrast sensitivity and stereoaucity are common among patients with PD. Freezing of gait in patients with PD is usually refractory to medications but may respond to visual cues. To see if there was a relationship between the visual deficits and freezing of gait, 96 consecutive patients with PD were evaluated for contrast sensitivity and stereoaucity and with a self-report of freezing of gait, but no significant correlation between the symptoms and visual function was seen (Wielinski CL, St. Louis Park, MN, P02.020).

In a retrospective study, 11 patients who met established diagnostic criteria for possible progressive supranuclear palsy (PSP) were compared with 8 patients with possible PD and 9 normal control subjects to identify findings that might help diagnose PSP. Neuro-ophthalmic findings that differentiated PSP from PD included slowed horizontal saccades (0.006), the presence of square wave jerks (SWJ) (0.001), apraxia of eye lid opening (0.029), abnormal vertical optokinetic nystagmus (OKN) (0.001), lid-retraction stare (0.001), blink rate (0.021), and light sensitivity (0.021). PSP could be distinguished from PD with 100% sensitivity and specificity by the presence of two of the following features: greater than 5 SWJ, abnormal downward OKN, and lid retraction. Only 1 subject with PSP had the diagnosis confirmed at autopsy. Although the results seem credible, the clinical diagnosis of PSP may be inaccurate and the findings in this study need to be verified with pathologic studies (Hills W, Salt Lake City, UT, P05.042).

**OPTIC NEURITIS AND MULTIPLE SCLEROSIS**

A survey assessing the evaluation and management of optic neuritis (ON) by neurologists and ophthalmologists in 7 countries was reported. In all countries, patients present more frequently to ophthalmologists and are subsequently referred to neurologists. Evaluation and management of ON varies among countries. Of the patients with ON, 70%–80% undergo brain MRI, and sometimes lumbar puncture (mostly in Europe and Thailand). Although most patients...
receive acute treatment with intravenous steroids, 17.5% of United States neurologists and 17.6% of ophthalmologists still prescribe oral prednisone (1 mg/kg/day) compared with 32% of neurologists and 26.7% of ophthalmologists outside the United States. In all countries, corticosteroids are often prescribed for reasons that are contrary to those in published studies: improving final visual acuity or decreasing the long-term risk of developing multiple sclerosis (MS). Disease-modifying agents are prescribed outside of local official recommendations by 20%–30% of physicians. The authors concluded that interpretation and application of evidence-based medicine generated by United States–based clinical trials vary among countries, guidelines are adapted to local health care systems and access to imaging and drugs, and the same mistakes and misinterpretations of studies are made in many countries (Biouss V, Atlanta, GA, S19.005).

Pathologic and clinical studies of MS and ON have suggested that fibers of the papillomacular bundle, which lie temporally in the retinal nerve fiber layer (RNFL), are particularly vulnerable to axonal degeneration. Patients with MS and disease-free control subjects had ocular coherence tomography (OCT)-3 to measure RNFL thickness and tests of low-contrast letter acuity and high-contrast coherence tomography (OCT)-3 to measure RNFL thickness >1.1, comparing affected eyes either to the fellow unaffected eyes or to the upper 95th percentile of control eyes. RNFL loss was judged if >3 sectors were thinner than the 5% lower limit of controls or if 2 sectors were >10 mm thinner than same sectors of fellow eyes. Compared with control eyes, 11 (31%) of affected eyes but no fellow eyes had swelling. Compared with fellow eyes, 23 (85%) affected eyes were swollen. The number of swollen sectors did not correlate with MRI optic nerve lesion site or extent or baseline vision. At 1 month, swelling remained in 4 (14%) affected eyes compared with control eyes and in 10 (50%) affected eyes compared with fellow eyes. At 1 month, RNFL loss developed in 54% compared with fellow eyes and in 24% compared with control eyes, and RNFL loss occurred in 50% of eyes still swollen. GDx was also used in this study and showed findings similar to those with OCT (Kupersmith M, New York, NY, S19.004).

A study reported RNFL thickness measured by OCT in 58 patients with MS (24 relapsing-remitting, 24 primary progressive, and 10 secondary progressive) with no history of ON. Patients with MS had thinner RNFLs in all four quadrants (mean: P # 0.001, temporal: P # 0.001, superior: P # 0.001, nasal: P = 0.003, and inferior: P # 0.001). Compared with control subjects, RNFL was reduced in relapsing-remitting MS (95 mm, P = 0.002), secondary progressive MS (84 mm, P # 0.001), and primary progressive MS (88 mm, P # 0.001). There was a significant reduction in the RNFL in secondary progressive MS compared with relapsing-remitting MS (P = 0.017). In addition, RNFL thinning was correlated with the Expanded Disability Status Score (EDSS) (r = 0.311, P = 0.018). Low-contrast letter acuity was significantly reduced in primary progressive MS compared with relapsing-remitting MS (P = 0.022) and was correlated with the decrease in RNFL thickness (r = 0.432, P # 0.001). These results suggest that RNFL is reduced in patients with MS without ON. OCT is a useful tool for monitoring axonal loss in the different forms of MS and could help in diagnosis of puzzling cases of MS, including the primary progressive variant (Meyniel C, Paris, France, P05.031).

High-dose intravenous methylprednisolone (IVMP) decreases the severity and duration of clinical relapses of MS, and prior studies have shown that high-dose oral corticosteroids have equivalent bioavailability and clinical efficacy. Forty patients with MS within 2 weeks of a clinical relapse with at least one contrast-enhancing MRI lesion were randomly assigned to receive either 1 g/day oral methylprednisolone (OMP) or IVMP for 5 days. At 28 days, the two groups showed significant reductions in enhancing lesions and similar clinical improvement, with no difference in tolerability, suggesting that OMP is as effective as IVMP for acute relapses in patients with MS (Martinelli V, Milan, Italy, P02.135).

A few studies dealt with neutralizing antibodies (NAb) in patients with MS treated with interferon. In the BENEFIT (Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment) trial, NAb titers were measured using the in vitro MxA assay every 6 months in 277 patients. Data were available for all patients 3 years after randomization. Over 3 years, NAb titers >1:20 NY/mL were detected at least once in 88 (31.8%) patients; 41 (46.6%) patients reverted to NAb-negative status by the
third year of the trial. There was no significant relationship between NAb titer and time to develop clinically definite MS (CDMS) or time to disability progression (Freedman M, Berlin, Germany P02.148). Another study identified 41 patients under continuous treatment with interferon [IFN]-b who were NAb-positive for at least 12 months and reverted to being NAb-negative for at least 12 months. These investigators studied 64 matching patients who had remained seronegative during 36 months. During the NAb-positive period, the annualized relapse rate was 0.77 compared with the annualized relapse rate of 0.43 in the permanently NAb-negative patients in matched periods of observation [P = 0.008]. Patients who reverted to a NAb-negative state regained a treatment effect with a relapse rate [0.43] similar to that observed in the permanently NAb-negative patients [0.4] in corresponding time periods [P = 0.67]. The investigators concluded that NAb positivity reduced the therapeutic effect of IFN–1b significantly. When NAb positivity disappeared during continued treatment, patients regained the full effect of INF–1b therapy [Sorensen P, Copenhagen, Denmark, P02.153].

A study investigated gray matter (GM) and white matter (WM) atrophy in MS. There were 73 patients (29 clinically isolated syndrome [CIS]; 33 relapsing-remitting MS [RRMS], and 11 secondary progressive MS [SPMS]) with a mean of 20.0 years from disease onset. Disability in patients was assessed by EDSS and MS Functional Score Composite score (MSFC). Three-dimensional T1 brain magnetic resonance images were obtained on a 1.5-T scanner and from these WM (WMF) and GM fraction volumes (GMF) were derived using SPM2 (statistical parametric mapping). GM and WM atrophy was significantly greater in patients with MS than in control subjects. There was significantly more GM atrophy in SPMS vs RRMS and in RRMS vs CIS. GMF (but not WMF) correlated with EDSS (r = 0.48, P ≠ 0.001) and MSFC (r = 0.59; P ≠ 0.001). The authors concluded that GM atrophy is greater than WM atrophy in patients with MS of relatively long disease duration (~20 years). In addition, GM atrophy seems to be more closely related to disability and disease subtype (Fisniku L, London, UK, S32.001).

A report of 30 children younger than 10 years with MS showed that the mean onset age was 4.9 years, 60% were female, and the most common presentation was an acute disseminated encephalomyelitis (ADEM)-like picture. Fifteen children presented with a CIS: brainstem-cerebellar 20%, transverse myelitis 13%, ON 10%, and motor syndrome 10%. After a mean follow-up of 8.3 years, 67% of children had RRMS, 30% had SPMS, and 3% had the Marburg variant. The mean number of relapses was 2.15 in the first year and 3 in the second year of disease. The median time from onset to disability scores of 3, 4, and 6 were 2.8, 3.3, and 5 years, respectively. This group showed a high relapse rate and rapid onset of disability (Tenenbaum S, Buenos Aires, Argentina, P03.024).

**NEUROMYELITIS OPTICA**

A pathologic study sought to determine whether neuromyelitis optica (NMO) hemispheric cerebral lesions demonstrate similar complement and aquaporin 4 (AQP4) expression as has been reported for optic nerve and spinal cord NMO lesions. Cerebral lesions from 2 patients with NMO (n = 4 lesions) and 13 patients with MS (n = 57 lesions) were analyzed via routine neuropathologic stains and immunohistochemical analysis against myelin, immune complexes, and AQP4 and compared with optic nerve and spinal cord lesions in 9 patients with NMO. All patients with NMO were seropositive for NMO IgG antibody. NMO cerebral lesions resembled NMO optic nerve and spinal cord lesions, including the presence of active demyelination, cosinophilia, and cavitation. Vasculocentric, periependymal immune complex deposition and AQP4 loss were noted as well. These characteristics were in contrast to those of cerebral and periventricular MS lesions, in which AQP4 expression was increased or retained in the periventricular ependymal lining (Roemer S, Rochester, MN, S27.003).

NMO has shown mechanisms in common with myasthenia gravis (MG) in that IgG in both disorders triggers antigenic modulation and complement activation. Sera submitted to the Mayo Clinic Neuroimmunology Laboratory (1981–2007) in 16 patients who met clinical diagnostic criteria for both NMO and MG were identified. All were women and were seropositive for NMO IgG and muscle acetylcholine receptor (AChR) antibody (13 of 14 tested were confirmed for AQP4-specific IgG). Fifteen patients (94%) had generalized MG; in 1 patient MG was restricted clinically to extraocular muscles. None had chest CT evidence of thymoma. Eleven patients (69%) had undergone thymectomy (9 with hyperplasia and 2 normal). All benefited from conventional therapy for MG; 12 had a remission. In 15 patients (94%) MG onset preceded NMO (mean interval 11.6 years; range 0.5–30). Fourteen patients had NMO and 2 had recurrent longitudinally extensive transverse myelitis without ON. Three patients (19%) had MRI brain abnormalities, predominantly diencephalic and brainstem. This study suggests a link between NMO and MG (Chan K, Rochester, MN, S27.006).

**CEREBROVASCULAR DISEASE**

Twenty-one patients with superior sagittal sinus thrombosis were reviewed to identify radiologic factors associated with hemorrhagic infarcts seen in 11 patients (52.4%). Nine patients (81.8%) in the hemorrhagic infarct group did not have evidence of collateral venous drainage compared with 3 (30%) in the nonhemorrhagic infarct
group (relative risk [RR] 2.7; 95% confidence interval [CI] 1.0–7.3, P = 0.019). Thrombus volume was not associated with hemorrhagic infarct (Muppidi, S, Wayne, PA, P03.123).

Prior studies suggest a higher mortality in patients with ischemic stroke admitted to hospitals on weekends and treated with intravenous tissue plasminogen activator (tPA) (“weekend effect”). A study of weekend vs weekday mortality in 286 patients at 2 university comprehensive stroke centers showed that weekend patients had 12.1% (13 of 107) in-hospital mortality compared with 10.1% (18 of 179) in the weekday group (P = 0.68). This negligible difference suggests that a comprehensive stroke center may erase the weekend effect (Albright K, La Jolla, CA, P01.043).

Of 432 consecutive patients with stroke, 17 were identified as having smoked cannabis within 30 minutes of symptom onset and had positive urine drug screen results. The mean age was 41 years. Two patients (both adolescents) died, and pathologic examination revealed hemorrhagic cerebellar infarction without embolus or vasculitis. Although not a controlled study, this report raises the possibility of a link between smoking cannabis and stroke (Singh NN, St. Louis, MO, P01.053).

A retrospective study compared emergency carotid endarterectomy (CEA) with intravenous thrombolysis (IVT) in acute internal carotid occlusion. The internal carotid artery recanalization rate was significantly higher in patients undergoing CEA (86.2%) than in those undergoing IVT (15.0%) (P # 0.0001). Moreover, a favorable 1-year clinical outcome was significantly more frequent in patients undergoing CEA (48.3%) than in those undergoing IVT (20.0%) (P = 0.044). The patients undergoing surgery were younger and had less deficit. However, when the analysis was restricted to the subgroups of patients with admission NIH Stroke Scale (NIHSS) scores of 10–20, no significant difference in age (P = 0.07) and sex distribution (P = 0.43) was found; good 1-year clinical outcome was seen in 35.7% of patients undergoing CEA versus 14.3% of those receiving IVT in this subgroup (P = 0.19). CEA may be a better treatment option, but because this study was retrospective, it is difficult to sort out the features that directed the treatment decisions (Herzig R, Lausanne, Switzerland, P01.164).

A retrospective study of 100 autopsy-verified cases of severe stroke showed a high percentage of pulmonary embolism in 38% of 76 patients with hemispheric infarcts and in 46% of 24 patients with brainstem infarcts. Pulmonary embolism was the cause of death in 5% of patients with hemispheric infarcts and in 29% of those with brainstem infarcts (P # 0.01) (Piradov M, Moscow, Russia, P02.005).

The frequency of cerebral venous and dural sinus thrombosis occurring during the fasting month of Ramadan was compared with that of such events occurring at other times. In 3 neurologic centers over a 5-year period 33 patients with venous strokes were evaluated during Ramadan and 129 during other months. The mean number of new cases during the month of Ramadan was 5.5 compared with 1.95 in other months. The authors concluded that fasting increases the frequency of venous thrombosis (Saadatnia M, Isfahan, Iran, P02.007).

A single institutional study reported 131 consecutive cases of cerebral artery dissection not associated with major trauma. In this cohort, 64% were men and 36% were women, with a mean age of 44. Risk factors included hypertension (29%), smoking (28%), migraine (12%), and minor trauma (29%). Presentations included 56% stroke, 15% transient ischemic attack (TIA), and 5% subarachnoid hemorrhage. No cerebrovascular events affected 24% of patients, who presented with headache (52%), Horner syndrome (42%), cervical pain (22%), tinnitus (8%), and cranial nerve palsy (8%). Extracranial dissection occurred in 56%, intracranial dissection in 28%, and both extra- and intracranial dissection in 16%. The carotid artery was involved in 75%, the vertebral artery in 17%, the basilar artery in 2%, and the posterior inferior cerebellar artery in 2%. Treatment consisted of anticoagulation in 55%, antiplatelet agents in 42%, and endovascular procedures in 3%. At follow-up, 87% had no or mild disability, 11% had moderate to severe disability, and 2% died (Falcone GJ, Buenos Aires, Argentina, P02.010).

**IDIOPATHIC INTRACRANIAL HYPERTENSION**

A study from three institutions compared the clinical characteristics in men and women in 721 consecutive cases of idiopathic intracranial hypertension (IIH). Men comprised 9%. As their first symptom of IIH, men were less likely to report headache (55% vs 75%, P # 0.001) but more likely to report visual loss (35% vs 20%, P = 0.005). Fewer men developed headache (79% vs 89%, P = 0.01) and fewer reported tinnitus (26% vs 38%). Visual acuity (VA) and visual fields (VF) at presentation and last follow-up were significantly worse among men. The relative risk of severe visual loss (defined as visual acuity poorer than 20/200 or a visual field perimeter of ≥20 degrees) for men compared with women was 2.1 for at least one eye (95% CI 1.4-3.3, P = 0.002) and 2.1 (95% CI 1.1-3.7, P = 0.03) for both eyes. Men were also more likely to have sleep apnea (24% vs 4%, P # 0.001) (Bruce B, Atlanta, GA, S19.003).

A retrospective chart review of 23 adult patients with IIH sought to determine whether weight gain correlated with clinical recurrence. Body mass index (BMI) was calculated at presentation, at the time of resolution of signs/symptoms, and at recurrence. BMIs for patients with IIH (n = 23; 92% female; age 35 6 9 years) at presentation,
Initial resolution, and recurrence were 33.6, 33.6, and 36.7 kg/m², respectively. Mean difference between presentation and initial resolution BMI was 6.3 kg/m², whereas the difference between initial resolution and recurrence BMI was +7.4 kg/m² (consistent with weight gain). BMIs at recurrence were significantly higher than those at initial resolution (P = 0.01, paired t test) and those at presentation (P = 0.01). No significant difference was noted between BMIs at presentation and initial resolution (P = 0.81). Average rate of BMI gain between initial resolution and recurrence was 4.4 kg/m²/year (range 2.2 to 15.8). The investigators concluded that IIH recurrence is associated with a significant BMI increase compared with BMIs at presentation and initial resolution. Patients with resolved IIH should be advised that weight gain increases the risk of recurrence (Ko M, Philadelphia, PA, P05.025).

LEBER HEREDITARY OPTIC NEUROPATHY
A small subset of patients with Leber hereditary optic neuropathy (LHON) have a negative test for the three primary mitochondrial DNA (mtDNA) point mutations (11778/ND4, 3460/ND1, and 14484/ND6). Eight such patients were investigated with complete mtDNA sequence analysis. Conservation analysis was also performed using a global alignment of 143 sequences from different species. All cases were consistent with a rare mtDNA mutation fulfilling the criteria for being pathogenic. Three patients were found to have the 14568/ND6 mutation, previously reported in a few patients with LHON. The 14459/ND6 mutation (haplogroup J1c), which was previously associated with LHON/dystonia, was found once. In addition, single occurrences of the 3700/ND1 (haplogroup H), 4171/ND1 (haplogroup J2b), 10663/ND4L (haplogroup L2a), and 14495/ND6 (haplogroup H) mutations were found. They were all reported previously in single (3700/ND1) patients or in very few patients. In a few instances, heteroplasmy was identified in maternal relatives, indicating a recent mutational event. This study confirms that about 10% of patients with LHON have rare primary mtDNA mutations (Amati-Bonneau, P, Strasbourg, France, P05.026).

PARANEOPLASTIC DISEASE
Two patients who had presented with narcolepsy and cataplexy and were found to have neuroblastomas were reported. One was a 3-year-old girl who subsequently developed opsoclonus/myoclonus. The second was a 2-year-old girl who also presented with weakness caused by Lambert-Eaton myasthenic syndrome (Sinsioco C, Kiev, Ukraine, P03.005).

VESTIBULAR DISORDERS
A cross-sectional study of emergency department (ED) visits from the National Hospital Ambulatory Medical Care Survey reviewed patients with the reason-for-visit code of vertigo/dizziness. In this study, 7,925 patients with dizziness comprised 3% of ED visits over 12 years. These patients were often polysymptomatic with other complaints being nausea/vomiting (19%), craniocervical pain (13%), malaise/fatigue (12%), and neurologic symptoms (9%). Chest pain, dyspnea, respiratory symptoms, abdominal pain, syncope, bleeding, palpitations, and fever/chills were...
common, with one or more symptom affecting 25%. Auditory/otologic (2.3%) and psychiatric (2.0%) complaints were uncommon. Diagnoses fell into the category of otologic/vestibular (27%), cardiovascular (21%), respiratory (12%), metabolic (11%), neurologic (11%, including 4% cerebrovascular), injury/poisoning (11%), psychiatric (7.5%), digestive (7.4%), and genitourinary (5%). Dangerous cardiovascular causes were diagnosed with comparable frequency among patients with dizziness as among patients with syncope (angina/myocardial infarction, 2.2% vs 2.8%; arrhythmia, 3.7% vs 4.5%). The authors concluded that among patients with dizziness who present to an ED, dizziness is rarely monosymptomatic, is rarely attributable to a vestibular disorder, and is more likely to be associated with cardiovascular and medical causes, including dangerous ones such as myocardial infarction and arrhythmia (Newman-Toker DE, Baltimore, MD, S19.001).

**FACIAL NERVE DISORDERS**

A retrospective review of 26 children with facial palsy examined over a 10-year period (11 boys and 15 girls) showed that 6 had symptoms of a preceding upper respiratory infection. Their ages ranged from 2 months to 18 years (mean 12 years), and 76% were older than 12 years. One child had an elevated Lyme titer. Neuroimaging was performed in 14, and revealed 1 case each of pontine glioma, epidural abscess, and cholesteatoma. In this group, 17 (65%) of 26 were treated, 5 with oral corticosteroids, 10 with corticosteroids and acyclovir, and 2 with acyclovir alone. Treatment was started within 72 hours in 12 of the 17 children. The time to recovery was no different in the treated and untreated groups. The extent of recovery was not reported. Although the authors conclude that treatment is not useful in children with Bell’s palsy, it would seem that this study is much too small to draw such a definitive conclusion (Thomas B, Cleveland, OH, P03013).

A report described a family with 5 cases of hemifacial spasm in 4 successive generations. All were women, 3 with left and 2 with right spasms, in an apparently autosomal dominant pedigree with incomplete penetrance. Onset was in the sixth decade in 4 and in the fourth decade in 1. Among the 4 who underwent brain MRI, only 1 showed abnormal results (a tortuous basilar artery that did not appear to compress the facial nerve) (Nestrasil I, Olomomouc, Czech Republic, P03.057).

**INFECTIONS**

A report described the first case of extracranial involvement of the twelfth nerve and the recurrent laryngeal branch of the tenth nerve (ipsilateral paralysis of the vocal cord, soft palate, and tongue, or Tapia’s syndrome) caused by cat scratch disease. In this patient, a cervical lymph node biopsy revealed chronic caseating granulomas with neutrophils. Oral erythromycin treatment was associated with partial recovery. Traditional causes of Tapia’s syndrome include injuries of the high neck, complications during airway access, arterial dissection, infections or tumors of the parotid gland, and other neck tumors (Cardoso FM, Rio de Janeiro, Brazil, P01.115).

A case report raised the issue of using corticosteroids in the treatment of Lyme disease. A woman with right peripheral facial palsy and a disseminated macular ring-like rash with positive Lyme IgM antibody and normal results on a CSF examination, did not improve after a 5-day course of ceftriaxone and doxycycline. With the addition of 80 mg of prednisone daily, the facial palsy and rash disappeared almost completely within 1 day (Ahmed SN, Elizabeth, NJ, P01.116).

**PRION DISEASES**

To assess the value of MRI in distinguishing Jakob-Creutzfeldt disease (CJD) from rapidly progressive dementia (RPD) of other causes, 90 subjects referred for CJD had brain MRI read by 2 neuroradiologists masked to the clinical diagnosis. All CJD patients had GM hyperintensity (diffusion imaging > FLAIR) in neocortical, limbic, or subcortical regions but never in limbic regions alone. Apparent diffusion coefficient (ADC) maps confirmed diffusion restriction in all subcortical regions only in patients with CJD. In the non-CJD group, the GM abnormalities were commonly limbic alone (FLAIR > diffusion imaging); none of the 10% of patients with subcortical hyperintensities had subcortical diffusion restriction on the ADC map. Sensitivity and specificity for CJD were 93.8% and 72.4% (reader 1) and 95.8% and 100% (reader 2), respectively. After consensus review, sensitivity and specificity for CJD were 97.9% and 100%. The pattern of FLAIR/diffusion imaging hyperintensity can differentiate CJD from other RPDs with high sensitivity and specificity, and the authors make the point that MRI should be included among the diagnostic criteria for CJD (Vitali P, Milano, Italy, IN2-2.005).

The 4th Asian Neuro-ophthalmological Society Meeting was held in Taipei, Taiwan, on May 15–17, 2008. This was the first meeting of this society to be held outside Japan.

Among the 287 participants, there were 240 from Taiwan, 13 from Japan, 10 from Indonesia, 7 from the United States, 6 from the Philippines, 4 from Korea, 2 each from China and Thailand, and 1 each from Singapore, Afghanistan, and Pakistan.

There were 67 posters and 13 free papers, as well as 6 symposia covering optic nerve disorders, basic ophthalmic research, ocular motility, injury neuroprotection and neuroregeneration, central nervous system diseases, and systemic diseases.

A highlight of the meeting was the second “Walsh-in-Asia” clinicopathologic case conference, begun at the 3rd ASNOS meeting in Tokyo in 2006. Modeled after the Walsh Society meeting in North America, it was moderated by Satoshi Kashii, MD (Osaka, Japan) and Jonathan Trobe, MD. The 5 cases selected by the organizing committee included 3 from Taiwan and 1 each from Indonesia and Japan. Guest neuroradiologist Dr. Mu-Huo Teng from Taiwan and guest neuropathologist Dr. Edwin Munoz from the Philippines provided illuminating commentary and enrichment material. The conference was enthusiastically received and will continue as an ASNOS tradition.

Among the special features of the meeting were a glove puppet show and a karaoke show. The meeting organizers were delighted at the strong attendance and the high level of the scientific material, signs that ASNOS is flourishing. The next meeting will be on November 15, 2009, in Tokyo.

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Delayed Third Cranial Nerve Palsy After Aneurysm Wrapping

Third cranial nerve palsy after aneurysm wrapping may be caused by damage to the nerve during surgical dissection, perianeurysmal inflammation related to the cotton used to wrap the aneurysm, or, if fibrin glue is also used, adherence of the wrapping material to the nerve. In almost all cases, the palsy occurs immediately after surgery.

We recently examined a 64-year-old woman who developed a third cranial nerve palsy on the side where, nearly 1 year earlier, she had undergone clipping of a 14-mm aneurysm located at the junction of the internal carotid and posterior communicating arteries.

At the time of surgery, a small residual area at the aneurysm base had to be wrapped with cotton and secured with fibrin glue. Intraoperative angiography had confirmed almost complete obliteration of the aneurysm. Postoperatively, the patient had no neurologic or visual deficits. During the year after surgery, she experienced two brief episodes in which, when looking in a mirror, she noticed that her left pupil was dilated. She never had double vision or drooping of her left upper lid at that time.

Eleven months after surgery, the patient sustained moderate trauma to her left orbit after she slipped while pushing a metal dolly and struck her head against the handle. She did not lose consciousness or sustain any facial lacerations, but she did develop significant swelling and bruising of the left orbit and face.

As the facial swelling resolved during the next month, she noticed binocular double vision and was found to have a partial left third cranial nerve palsy that became complete over the next 5 months. MRI and catheter angiography showed no changes from previous intraoperative imaging, but a lumbar puncture showed an increased protein concentration of 98 mg/dL. The patient was treated with 1 g of intravenous methylprednisolone per day for 3 days, followed by 60 mg of prednisone per day. Two weeks after treatment was started, the patient’s third cranial nerve palsy began to improve and continued to improve until the patient stopped treatment because of side effects.

Two other cases of delayed third cranial nerve palsy after aneurysm wrapping have been reported (1,2). Onoue et al (1) described a patient who developed a progressive third cranial nerve palsy 19 months after clipping and wrapping of an aneurysm at the junction of the ipsilateral internal carotid and posterior communicating arteries (2). No treatment was offered. Despite partial improvement in ptosis over the next year, palsy of the superior, medial, and inferior rectus muscles was still present 4 years later.

We believe that in our patient the combination of wrapping material and fibrin glue resulted in slight adhesion of the aneurysm to the superior aspect of the third cranial nerve that was then exacerbated by the head trauma. Whatever the mechanism, our patient illustrates the fact that such delayed postoperative complications can occur many months after otherwise uncomplicated aneurysm treatment, particularly when clipping and wrapping are used. Corticosteroid treatment may be effective.

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Anticholinergic Esotropia

In this journal, Oh and Shin (1) recently described a patient who developed esotropia and mydriasis 7 days after beginning treatment with haloperidol and benztropine mesylate. They attributed the esotropia to convergence caused by the excessive accommodative effort required to overcome the anticholinergic effects of these medications. Another case of anticholinergic esotropia has just been reported in a 5-year-old girl taking oxybutynin (Ditropan) for enuresis (2). We recently examined a patient whose clinical history casts further light on this phenomenon.
A 29-year-old woman presented with a 1-month history of horizontal diplopia. She had had esotropia in early childhood that gradually evolved into a consecutive exotropia. She also had a history of schizophrenia, depression, and anxiety and was being treated for these conditions with escitalopram (Lexapro), benztropine mesylate (Cogentin), quetiapine (Seroquel), aripiprazole (Abilify), hydroxyzine pamoate (Vistaril), cyclobenzaprine (Flexeril), and lamotrigine (Lamictal). She had asthma and used an albuterol inhaler.

Ophthalmologic examination revealed a distance visual acuity of 20/30 in the right eye and 20/25 in the left eye. Pupils measured 6 mm bilaterally in dim illumination and reacted sluggishly to direct light, constricting only to 5 mm. Dynamic retinoscopy showed decreased accommodation bilaterally. Horizontal optokinetic testing showed asymmetrical monocular responses that were greater nasally than temporally, indicating ocular misalignment within the first year of life. Prism and alternate cover testing showed an esotropia of 20 prism-diopters when fixating on a distance target and 45 prism-diopters when fixating on a near target. Cycloplegic refraction showed no significant refractive error. She had no latent nystagmus, dissociated vertical deviation, or cross fixation. Extraocular movements were full with 1+ inferior oblique muscle overaction bilaterally. Anterior and posterior segment examinations were normal.

We informed the patient that she would probably require strabismus surgery. However, we suspected that the anticholinergic medication might be contributing to the esotropia, especially benztropine mesylate, hydroxyzine pamoate, and cyclobenzaprine. We discussed the issue of overmedication with her psychiatrist, who elected to discontinue her quetiapine, lamotrigine, cyclobenzaprine, aripiprazole, and hydroxyzine pamoate. The dose of benztropine mesylate was reduced.

On follow-up examination 2 months later, the patient reported that her diplopia had resolved. Dynamic retinoscopy showed improved accommodation. Prism and alternate cover testing now showed a constant exotropia of 12 prism-diopters when fixating at distance and 9 prism-diopters when fixating at near.

Our patient’s treatment with multiple psychotropic medications had converted her long-standing exotropia to an esotropia with associated diplopia. Reducing the anticholinergic medications allowed her eyes to revert to their baseline exotropic position and produced resolution of her diplopia.

We agree with the pharmacological mechanism proposed by Oh and Shin (1) in which anticholinergic-induced paresis of accommodation leads to excessive accommodative effort with a corresponding excess of accommodative convergence. In children with accommodative esotropia, it is common to see a large-angle esotropia develop in the waiting room after administration of topical anticholinergic medications to dilate the pupils. Conversely, phospholine iodide, a cholinesterase inhibitor that enhances the effect of acetylcholine on the ciliary muscle, is used in topical form to eliminate small-angle esotropia (3).

Given that so many widely used medications have anticholinergic properties, it is surprising that anticholinergic esotropia is not reported more regularly. Our patient’s preexisting strabismus and absence of fusion rendered her susceptible to this complication. As Oh and Shin (1) noted, their patient may have also had several predisposing neurologic factors. The need for an intrinsic predisposition for anticholinergic esotropia would best explain the striking rarity of this complication. Since examining our patient and reading the similar report by Oh and Shin (1), we have begun routinely screening for anticholinergic medications in patients with esotropia before planning strabismus surgery.

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Scope: This book is a distillate of the full three-volume, 3,500-page 6th edition of Walsh and Hoyt’s Clinical Neuro-Ophthalmology. It is designed to cover the most clinically relevant aspects of neuro-ophthalmology. There are five main sections: 1) Afferent Visual System; 2) Pupil; 3) Efferent System; 4) Eyelid; and 5) Nonorganic Disease.

The afferent visual system section comprises 13 chapters and about half of the book’s pages. The content is extremely comprehensive and well organized into chapters on examination techniques, anatomy, various optic nerve pathologic conditions, chiasmal/retrochiasmal lesions, and central disorders of vision.

The pupil section contains chapters on examination and disorders of the pupil, accommodation, and lacrimation.

The efferent system section includes chapters on examination (Chapter 16), chapters that divide efferent disorders by location (supranuclear and internuclear, nuclear and infranuclear, neuromuscular junction, and muscle), and a final chapter covering nystagmus and other motility abnormalities. There are clinical photographs of virtually every significant ocular motility abnormality, and these are well correlated with imaging studies and schematic diagrams.

The final two sections comprise 1 chapter each: eyelids and nonorganic visual loss. The eyelid chapter covers anatomy and abnormalities of both eyelid opening and closure. The nonorganic disease chapter contains a nice introduction concerning correct terminology followed by sections on the nonorganic afferent system, efferent system, pupil, accommodation, and eyelid entities.

Strengths: This is a very comprehensive but fairly succinct, clinically relevant, and useful text. The numerous illustrations, photographs, and schematic diagrams help to bring the conditions and concepts to “life.” Frequent correlation with neuroimaging facilitates better comprehension of the material.

Weaknesses: There are no references in the text and the reader is referred to the full Walsh and Hoyt text. Clearly including the references will lengthen the book, but I suspect not everyone will own the entire Walsh and Hoyt or at least not have both texts in the same location. It also would have been advantageous to have had the fundus photographs in color.

Recommended Audience: The recommended audience is neuro-ophthalmologists and neurologists and ophthalmologists with more than a passing interest in neuro-ophthalmology.

Critical Appraisal: Excerpting the most relevant material from this encyclopedic text is a tour de force. This is the choice for those with a special interest in neuro-ophthalmology.

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Eye Movement Disorders


Scope: The book is divided into 4 sections, the first covering the functional classes of normal eye movements (vestibular, optokinetic, saccadic, smooth pursuit, and vergence systems) and their neural pathways and the second through fourth sections covering clinical disorders of ocular motility. The second section covers involuntary eye movements such as nystagmus and saccadic intrusions. In the third and fourth sections, the approach to clinical eye movement disorders is localization based, covering supranuclear, internuclear, nuclear, and infranuclear lesions.

Strengths: The major strength of the manual is its presentation. It succeeds in dividing a formidable and complex topic into accessible and easy-to-read segments with reinforcement of the fundamental aspects of each eye movement disorder via ample use of color-coded boxes, tables, photographs, and anatomical illustrations. It is practical and clear, with a heavy clinical emphasis. A CD-ROM containing the complete text and eye movement videos of some of the disorders is included. All videos are cross-linked with the text. A very extensive index makes for easy localization of topics of interest.

Weaknesses: Although the book contains a selected bibliography for each chapter, none of the textual details
are directly referenced. The text is not intended to be exhaustive, and the reader who desires detailed, referenced coverage of the biology, physiology, anatomy, and clinical disorders of ocular motility may find the brief, bulleted topic coverage insufficient. For the inexperienced student, the lack of video legends may prove slightly challenging, as some of the abnormalities shown on the videos are subtle.

Recommended Audience: Neurology and ophthalmology residents and clinicians directly involved in evaluation of patients with ocular motility problems are likely to find this book most useful.

Critical Appraisal: The author has captured the fundamentals of ocular motility disturbances in an understandable and simple format. Much of the material is found in the esteemed text, The Neurology of Eye Movements by R. J. Leigh and D. S. Zee. The anatomic illustrations and emphasis on clinical recognition, in combination with the accompanying eye movement videos, will enable the reader to grasp and appreciate the knowledge presented and to improve diagnostic prowess in identification of clinical eye movement disorders.

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Clinical Neuro-Ophthalmology.
A Practical Guide

Ulrich Schiefe, MD, Helmut Wilhelm, MD, and William Hart, MD, PhD.
ISDN: 978-3-540-32706-6, $229.00.

Scope: This introductory text of neuro-ophthalmology is a translation of a 2003 German text entitled Praktische Neuroophthalmologie. It has extensive color illustrations and figures and includes a DVD with 37 videos of examination techniques and eye movements, as well as 6 animations of clinical signs. In addition, 5 posters are included, and there is 1 interactive teaching case.

Each of the 24 chapters is written by a combination of the 3 editors and 23 additional contributors. In addition to the expected chapters on taking a history, functional anatomy, perimetry, pupillary disorders, and optic disc changes, there are also chapters on electrophysiology, neuro-ophthalmic aspects of orbital disease, brain tumors relative to clinical neuro-ophthalmology, headaches from a neuro-ophthalmic point of view, drug-induced and toxic disorders in neuro-ophthalmology, pediatric neuro-ophthalmology, imaging, neurology, neurosurgery of the visual pathways, and radiotherapy for tumors of the anterior visual pathways. There is also a chapter on reading disorders. In view of the concise aspect of the book, many of these chapters are really quite short. However, there is an emphasis on take-home messages that are color-coded. The authors are specific about the intended audience, including comprehensive ophthalmologists and residents in training.

Strengths: The major strength is the inclusion of the DVD. It not only allows for rapid search of particular topics, but also permits the inclusion of ocular movement videos as well as some illustrations and animations of clinical examination techniques and findings. The graphics are presented simply, and the teaching points are direct. Another major strength of this volume is the emphasis and identification of “pearls.” The text is well organized and easy to go through. The authors do include newer technologies such as multifocal electroretinography (ERG).

Weaknesses: Some of the weaknesses are inherent in the attempt at keeping this volume short. The discussion of neurosurgery and radiology are extremely brief. The interactive case study is difficult to go through, and cost effectiveness is not adequately emphasized. The posters are helpful. The flow diagrams are impractical and confusing. I doubt that any are going to be posted on a wall! There are some non-mainstream neuro-ophthalmic concepts, including the idea that a temporal crescent lesion might be due to a temporal lobe lesion. Some of the illustrations are confusing. The videos could be of better quality, particularly those involving pupil problems.

Recommended Audience: This book is intended for residents or practitioners who are interested in a basic introduction. General ophthalmologists will find in this book convenient, easy-to-read explanations of the basics of neuro-ophthalmology. It is an improvement on the available texts in the wide use of illustrations and the inclusion of a DVD containing videos. It is not a substitute for encyclopedic texts and probably is not a volume that one would use for reference.

Critical Appraisal: The authors have admirably kept this text simple. They have well emphasized the important pearls of neuro-ophthalmology and have presented them in a readable format. Compared with other abbreviated introductions to neuro-ophthalmology, this book has the advantage of improved illustrations, identification of critical concepts, and inclusion of videos.

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Handbook of Pediatric Neuro-Ophthalmology

Kenneth W. Wright, MD, Peter H. Spiegel, MD, and Lisa S. Thompson, MD.
ISBN 0-387-27929-6, $64.95.

Scope: Pediatric neuro-ophthalmology is more than just neuro-ophthalmology of little people. The diseases are different from those of adults, with a greater prevalence of congenital malformations and genetic disorders. The approach also differs, particularly with regard to examination techniques and interaction with parents.

The multi-authored chapters of this handbook are taken from the neuro-ophthalmology section of Wright and Spiegel’s comprehensive hardcover book, Pediatric Ophthalmology and Strabismus (Springer, 2003).

This book does a wonderful job summarizing neuro-ophthalmic disorders seen in childhood. Topics covered include ocular motility disorders, congenital optic nerve abnormalities, cortical visual impairment, nystagmus, and neurodegenerative conditions.

As a paperback handbook measuring 10.25 cm × 17.5 cm × 2 cm, it can easily fit in a laboratory coat pocket, or doctor’s bag.

Strengths: Most of the authors are well-known pediatric neuro-ophthalmologists (Buckley, Phillips, Brodsky, Repka, and Borchert) whose expertise and ability to communicate are evident in their chapters.

Two outstanding chapters should be highlighted. Mintzer and Buckley’s extremely informative chapter on “Neurocranial Defects with Neuro-Ophthalmic Significance,” and Chernus-Mansfield’s refreshing chapter entitled “Breaking the News: The Role of the Physician” are both unique. The latter describes how crushing it is for parents to hear that their seemingly perfect baby is permanently blind.

Weaknesses: The intended audience for this book is not clear. It appears to be geared toward ophthalmologists. Thus, in the embryology chapter, the principal emphasis is placed on eye development and malformations rather than on brain development and central nervous system mishaps. There is very little information on the neurologic examination.

Because chapters were pulled from a larger book, some of them contain information that seems out of place in a neuro-ophthalmology book. In the low vision chapter, for example, there is advice for “the aphakic child” and “myopes.”

There are some errors and redundancies which could have been eliminated with careful editing. On p. 138 there is a figure of a middle-aged man with a third cranial nerve palsy, out of place in a pediatric neuro-ophthalmology book. Illustrations for recording nystagmus are presented in two separate chapters. Chiari II malformations are covered twice. Cerebral visual impairment is the topic in two chapters.

Recommended Audience: Students, residents, fellows, pediatric neurologists, and ophthalmologists who examine children with neuro-ophtalmic disorders would benefit from this book.

Critical Appraisal: Those who desire a handy source in the clinic will find this book very helpful. However, pediatric ophthalmologists will probably already have a copy of Wright and Spiegel’s more comprehensive hardcover book. Those wanting a more detailed reference textbook on pediatric neuro-ophthalmology may be disappointed.

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Neuro-Ophthalmology. Neuronal Control of Eye Movements

Andreas Straube, MD, and Ulrich Bu¨ttner, MD.

Scope: This book is a multi-authored monograph in the series entitled Developments in Ophthalmology edited by W. Behrens-Baumann. The aim of this volume is to present to clinicians and basic scientists the current state of research and clinical studies in the ocular motor system. The aim is also to promote a continuing interdisciplinary approach to further improve diagnostic methods and develop new therapies.

The book contains 10 chapters from 13 contributing authors, 39 figures, and 3 tables. It highlights our current understanding on the anatomy and mechanical properties of the ocular motor system, the neural basis of the vestibular-ocular reflex, saccadic, smooth pursuit, and vergence eye movements, and the contribution of the eyelid to eye movements. It also discusses the various techniques for recording eye movements and the current models of different eye movement subsystems. It concludes with a chapter on pharmacologic treatment of ocular motor disorders.

Strengths: The chapters in this book reflect the expertise of its authors, all knowledgeable in ocular motor control. Important topics are covered, and advances in different areas are well presented and referenced.
Weaknesses: A more in-depth treatment of the topics would be beneficial for someone who is not familiar with the ocular motor system; however, this is not the intention of this book, which focuses on recent advances in this field.

Recommended Audience: This book successfully reaches its target audience—ophthalmologists, neurologists, and basic scientists.

Critical Appraisal: This book is worthwhile reading for anyone who would like to become familiar with the latest developments in ocular motor research.

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Kenneth W. Wright, MD.

Scope: The text is intended to provide a “how-to manual” for the strabismus surgeon. The text offers much more than a simple color atlas. In the first third of the book, the author discusses basic diagnostic and nonsurgical management of subjects of interest to the strabismus surgeon ranging from amblyopia to cranial nerve palsies. The rest of the book covers basic surgical technique, procedures on each of the extraocular muscles, adjustable techniques, and methods to approach reoperations. In this third edition, there is a new chapter on strabismus surgery under topical anesthesia. As in the prior editions, this version is richly illustrated with line drawings and color photos of anatomy, eye movements, and surgical techniques. New in this edition are 15 videos on a DVD. Many of these videos are basic but helpful to the surgeon inexperienced in patient positioning, instrument placement, and tissue handling.

Strengths: There are not many textbooks that cover the practical details of strabismus surgery planning and performance. The videos are a special bonus.

Weaknesses: Neuroimaging in diagnosis of complex strabismus and planning of surgical treatment is restricted to three low-quality images. There is no discussion of theories of extraocular muscle pulleys and how these may affect management.

Recommended Audience: This necessarily tightly written text is most appropriate for residents, fellows, and surgeons who perform strabismus surgery infrequently. The experienced strabismus surgeon will find the text too basic.

Critical Appraisal: The publication of the third edition of this atlas fills a large void. The insights will assist surgeons in developing their surgical approaches, although they should remain receptive to alternative opinions.

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Strabismus Surgery and Its Complications
David K. Coats, MD, and Scott E. Olitsky, MD, Editors.

Scope: This book represents a detailed description of surgical indications, procedures, and complications. It covers ocular and orbital anatomy, techniques of strabismus surgery, and complications. A DVD that contains video footage of the surgical techniques complements the first part of the text.

The text is divided into two parts. The first part deals with the surgical management of strabismus. There are excellent chapters on surgically important anatomy, physiology of eye movements, indications for strabismus surgery, and surgical decision making. Preoperative and postoperative care and anesthesia considerations also have dedicated chapters. There is also a chapter on surgical equipment, operating room supplies, and patient preparation. Six chapters detailing techniques of surgery explain in detail techniques for performing standard extraocular muscle surgery. The individual chapters on muscle weakening and strengthening procedures are well written. There are also chapters on surgery of the inferior and superior oblique muscles and on transposition procedures. Finally, there are chapters dealing with adjustable suture techniques, unusual surgical procedures in strabismus, the use of Botox, and nonsurgical treatment of strabismus. The second part of the book is devoted to complications of strabismus surgery. There are chapters on common errors (inappropriate decision making, operating for the wrong surgical angle, and operating on the wrong muscle). Anterior segment ischemia, pyogenic granuloma, scleral perforation and penetration, and postoperative infection have individual chapters. Additional chapters deal with anesthesia-related complications, unexpected postoperative changes in alignment, and residual diplopia.
This section concludes with medicolegal aspects of strabismus surgery.

Strengths: This text is a wonderful complement to traditional surgical teaching. It is meticulous and impeccably documented with photographs. It is well written and well referenced. The photographs are of extremely high quality. The DVD is excellent in showing common surgical techniques.

Weaknesses: The text has few weaknesses. However, some of the more complicated special surgical techniques are not described in sufficient detail to allow the reader to feel comfortable in adopting them.

Recommended Audience: Ophthalmologists who perform strabismus surgery occasionally and residents will find this text useful. It is also a superb text for the pediatric ophthalmology fellow.

Critical Appraisal: This text book is an important contribution to the field. It will be widely used.

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Neurology Board Review. An Illustrated Study Guide

Nima Mowzoon, MD, and Kelly D. Flemming, MD, Editors.
ISBN: 978-0-8493-3791-8, $149.95.

Scope: This 1,000-page hard cover volume is designed to be a comprehensive source for neurologists studying to pass the certification written and oral examinations set by the American Board of Psychiatry and Neurology (ABPN).

There are many other books to consult for this purpose—most of them softcover, shorter, and relatively superficial. This is truly a hard-core production. It is in outline form, but that is its only real difference from a standard textbook. It is brilliantly organized and illustrated with superb anatomic drawings, schematic diagrams, pathologic specimens, flowcharts, and imaging studies. Although some of material is excerpted, a surprising amount is original.

There are 25 chapters, many written by the co-authors, who seem to be Mayo-trained clinicians of junior vintage. The remaining chapters are also anchored by Mayo trainees. The field of neurology is well-covered, and there is even an excellent chapter on the basic principles of psychiatry containing almost enough material to allow a trainee to pass the psychiatry section of the ABPN examination.

Strengths: I have read most of this material and find it stunningly informative and easy to absorb. The outline form helps to keep the text from wandering off the clinical margin. The text is grounded in solid pathophysiologic principles and evidence.

Weaknesses: Text in outline form is not for everyone, especially those going through this material for the first time. Also, multi-authored textbooks inevitably suffer from nonuniformity—some chapters are better than others. But the topics with which I was most familiar, particularly those in the neuro-ophthalmologic section, were remarkably free of error.

Recommended Audience: Although this book is designed for neurology trainees preparing for their certifying examinations, it should work very well for readers who know the pieces but are not sure how they fit together.

Critical Appraisal: This is not an off-the-cuff production. It is a serious work with high production values and careful editing. The two editors have nicely authored much of the text and solicited fine contributions from their co-authors. This is a valuable resource, not merely for those preparing for the certifying examination in neurology, but for those who are looking for a thoughtfully organized approach to complicated medical material.

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Fundamental Neuroscience for Basic and Clinical Applications, 3rd Edition

Duane E. Haines, PhD.

Scope: This is a comprehensive neuroscience textbook that integrates the basic sciences with clinical information. This new edition incorporates more on the clinical relevance of anatomy and physiology of the nervous system compared with previous editions. Each chapter is authored by experts in the various fields.

The book is divided into three sections. The first section, Essential Concepts, details development of the nervous system, cell biology, neurophysiology, and
neuronal communication. The second section, Regional Neurobiology, includes chapters dedicated to the ventricles and cerebrospinal fluid, meninges, cerebrovascular system, spinal cord, and each region of the brain. The last section, Systems Neurobiology, focuses on the somatosensory system, viscerosensory pathways, visual, auditory, and vestibular systems, olfaction and taste, the motor system, the basal nuclei, cerebellum, visual motor systems, visceral motor pathways, hypothalamus, limbic system, and cerebral cortex. The final chapter is an overview of the neurologic examination.

Strengths: This book is up-to-date and comprehensive yet concise and will have broad appeal to medical students, residents, and practicing physicians who wish to consult a reference for quick review of anatomy and physiology. The book is well organized and is beautifully illustrated, including many MRI scans. The authors use a “Synopsis of Clinical Points” at the end of each chapter, which helps to highlight important clinical issues. Purchase includes access to an online version.

Weaknesses: The clinical information is sparse, generally consisting of only one to two sentences per topic. The last chapter on the neurologic examination only covers basic aspects of the examination at a level appropriate for a medical student. Thus, this is not the book from which one can learn clinical neurology.

Recommended Audience: This book is best for medical students or undergraduate students taking a neuroanatomy course. In addition, this book could serve as a basic science reference for practicing physicians.

Critical Appraisal: This book provides a comprehensive and up-to-date yet concise account of the neurosciences. It is set apart from other books on similar topics by the fine drawings, and neuroimages.

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The Clinical Neuropsychiatry of Multiple Sclerosis, 2nd Edition

Anthony Feinstein, PhD.

Scope: This is a single-authored book reviewing the neuropsychiatric issues in multiple sclerosis (MS). It is divided into 12 chapters. Chapter 1 is a thorough but succinct overview of MS, which effectively sets the stage for the remainder of the material. Chapters 2–6 focus on the psychiatric issues seen in patients with MS, including depression and pseudobulbar affect. The author cites all of the available literature on this topic and provides useful recommendations. Chapters 7–12 focus on the cognitive issues in MS. This portion of the book covers natural history, testing methods, neuroimaging, and other dementias.

Strengths: This book represents the most comprehensive source on neuropsychiatric issues in MS. The second edition of this book is a welcome update on this complex but essential aspect of MS.

The author does a commendable job distilling the important and interesting aspects for the reader. The book is well written and edited. The chapters are well laid out with useful summary points.

Weaknesses: Given the complexity and breadth of material covered in Chapters 7–12, I think the author could have further crystallized the information. For example, in Chapter 9, which reviews the testing methods for cognitive impairment in MS, the author states that “To the uninitiated, these multiple acronyms may be confusing, if not irritating.” I agree, and would have welcomed a table to consolidate and classify these tests. In Chapter 12, the text regarding subcortical neuroanatomy could have been augmented with illustrations of pathways to provide the reader with a three-dimensional concept of the relevant pathways and their association with other brain structures (as was done in Chapter 5).

Recommended Audience: I would recommend this book to anyone caring for patients with MS, including physicians, nurses, and rehabilitation therapists. In addition, community advocates for MS would benefit from reading this book.

Critical Appraisal: The author provides us with the only comprehensive, up-to-date review of this important and often under-recognized aspect of MS. It will serve as a cornerstone for future publications on this topic.

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Minimally Invasive Neurosurgery

Mark R. Proctor, MD, and Peter M. Black, MD, PhD, Editors.
Scope: This book covers an important and evolving trend in neurosurgery, namely the minimally invasive approaches that have been developed to treat a variety of problems in novel and effective ways. These concepts have captured the imagination of surgeons, physicians, and patients, and they surely are here to stay.

The techniques covered are diagnostic and surgical. The chapters on diagnosis include MRI, proton magnetic resonance spectroscopy, intraoperative MRI, and functional brain mapping. Many of these topics are also pertinent to standard neurosurgical procedures.

The use of endoscopy is well described as a foundation for many of the applications covered in the second section. Endovascular neurosurgery is well described for the management of aneurysms and other cerebrovascular problems, using coils and stents and embolic agents. Image guidance using neuronavigational systems is covered, as are the techniques used to produce stereotactic lesions with radiofrequency current. There are also chapters on gene and viral therapy and on direct injection of agents into the brain.

The second section describes the application of these concepts in children, vascular diseases, tumors, brain and spine disorders, peripheral nerve disorders, and traumatic brain injury.

Strengths: This book provides an introduction to many of the new techniques that have allowed minimally invasive approaches. All topics are well described.

Weaknesses: It is difficult to be up to date in an evolving field, and this book lags in some areas.

Recommended Audience: This volume will be of interest to those desiring an overview of an evolving and innovative area of neurosurgery.

Critical Appraisal: This is a useful introduction for those interested in technological advances and their application to neurosurgical problems.

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The Massachusetts General Hospital Handbook of Neurology, 2nd Edition

Alice W. Flaherty, MD, PhD, and Natalia S. Rost, MD.

Scope: This is the second edition of this popular handbook, designed as a pocket reference guide to neurologic diagnosis and management. In addition to basic material on neuroanatomy, localization, and specific diagnoses, it includes sections on pharmacology, neuroimaging, and internal medicine. The intended audience appears to be primarily residents in neurology seeking quickly accessible information on the initial approach to neurologic conditions. Non-neurologists will find it useful as well.

The format is compact and organized alphabetically into sections on Admissions, Adult Neurology, Child Neurology, Drugs, Imaging, Medicine, and Procedures. The material within each section is also organized alphabetically. In addition to the table of contents and index, a list of neurologic and common medical emergencies is included on the flyleaf with page references. The material in each section is presented in outline format. Throughout the manual, there are excellent anatomic illustrations and useful tables presenting additional material in summary format.

Strengths: The authors have managed to include an enormous amount of information, covering basic and more specialized aspects of neurology. The outline of the neurologic examination will be particularly useful for students and non-neurologists. Essential features of a screening examination are underlined, although this feature is not carried through consistently. Additional information on the examination is included in sections on specific symptoms and syndromes. In general, the material from various specialties within neurology is well presented and reasonably comprehensive, with cross-references to other relevant sections. A particular strength is the succinct guidance on interpretation of neurodiagnostic findings in particular conditions. The sections on neuroimaging are particularly strong. The inclusion of information from closely related specialties such as neurosurgery and internal medicine is particularly useful for management in the inpatient setting, as are the sections on orders and procedures, appropriate in a work targeted primarily to residents.

Weaknesses: Inevitably in a manual of this type, the brevity required to cover a great deal of information in a small volume will occasionally lapse into the telegraphic. Not all references are clear, and some reflect primarily local practice in examination and management. Some of these less-standardized elements are presented without further clarification and will be particularly perplexing to the non-neurologist, examples being Wartenberg’s sign and the go/no go task. The algorithms to determine prognosis in coma or to administer tPA in acute stroke require more guidance than is available here. The sections on psychiatric disorders and “psychosomatic neurology” are marred by over-generalization and often glib advice. There are occasional
proof-reading errors, such as omission of page references in allusions to material elsewhere in the handbook, and rare factual errors. This reviewer found the occasional jocular asides on topics such as ‘‘MD jargon aphasia’’ and use of colloquialisms (‘‘snot’’) to detract from the overall practical and informative tenor of the material.

Recommended Audience: This will be most useful to residents in neurology and to those in fields related to neurology as a quick guidance in the initial approach to a wide range of neurologic problems. The succinct and practical guidance in neuroanatomy, differential diagnosis, and neurodiagnostics, particularly neuroimaging, will be welcomed.

Critical Appraisal: This handbook succeeds admirably in its stated aim ‘‘to quickly update and remind the reader.’’ The scope of the information that it contains is greater than would be expected for a pocket manual. It provides an informed clinical perspective in directing the initial approach to neurologic problems.

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Intracranial Arteriovenous Malformations

Philip E. Stieg, MD, PhD, H. Hunt Batjer, MD, and Duke Samson, MD.

Scope: This is a reference text intended for vascular neurosurgical and cerebrovascular fellows and practitioners. It is composed of 34 chapters from 85 different authors. A review of the list of authors reveals an excellent cross-section of experienced and mainly academically based neurosurgeons, complemented by neurocritical care intensivists, neuroanesthesiologists, and neuroradiologists. The subject matter is very comprehensive and well-balanced.

There are six well-organized sections: I, Anatomy and Physiology; II, Clinical Presentation and Diagnostic Evaluation; III, Basic Considerations; IV, Therapeutic Management; V, Special Problems; and VI, Future Considerations. The chapters presented within each of these sections are in depth and show good attention to the importance of arteriovenous malformation (AVM) localization and defining interventions, anesthesia considerations, clinical presentations, and outcomes. These chapters demonstrate an appreciation of the complexity of this disease and the characteristics that need to be taken into consideration. Thus, the book has direct clinical application and relevance rather than simply being a general discussion of the topic.

Strengths: The editors’ goal of ‘‘providing a thorough discussion of the scientific data in prose that is and understandable for clinical application’’ has been remarkably achieved. Highlights from each section include the following.

The chapters on surgical anatomy and hemodynamic properties contain concise and clinical relevant information. The surgical anatomy chapter is well integrated into those on therapeutic management. The chapter on the use of modeling to study AVMs for clinical and translational research applications adds a novel contribution by introducing material not normally found in this depth.

The chapter on radiographic diagnosis is particularly strong. The chapters devoted to general principles of surgical, endovascular, and radiosurgical approaches of treatment could easily be books in themselves. In the chapter on decision analysis for the asymptomatic lesion, the authors should be commended for their attempts to present this tool based on the morbidity/mortality rates for both the individual surgeon and an individual lesion.

The chapters on management of cerebral AVMs allow the reader to use the book as a reference for an individual clinical case. This section includes consideration of anesthesia, perioperative angiography, and the management of associated aneurysms, AVMs during pregnancy, treatment of pediatric AVMs, and the management of residual lesions after initial treatment.

The illustrations are well chosen. There are 8 pages of color illustrations that demonstrate important concepts of histopathology, gross pathology, neuroimaging, and surgical approaches.

The chapters are well-referenced, but, more importantly, there are numerous new insights based on the wisdom acquired from the vast experience and expertise of the authors.

Weaknesses: Some aspects of endovascular treatment could be expanded. For example, the discussion of Onyx embolization is quite superficial. In future editions the clinical presentation section should be expanded. There is one chapter devoted to natural history and a single page to nonhemorrhagic clinical presentations. The presentation of the erroneously diagnosed ‘‘migraine patient’’ with solely unilateral migraineous-type headaches needs to be emphasized as an important caveat in the presentation of the patient with headache.

Recommended Audience: This book is most suitable for neurosurgical and neuroradiology clinicians and their trainees, including residents and fellows.
Critical Appraisal: This book is an outstanding contribution. It is one of the few comprehensive books on this topic. The editors have done a superb job in editing the individual chapters to ensure comprehensive coverage without unnecessary overlap. The textbook will undoubtedly become an important reference for physicians involved in the diagnosis and therapeutic decision making for patients with cerebral AVMs.

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The Dementias 2

John H. Growden, MD, and Martin N. Rossor, MD, FRCP, Editors.

Scope: This volume provides an up-to-date and concise review of research on the current conceptualization of dementing illnesses. It focuses on recent progress and understanding of the etiology of the dementias based on molecular mechanisms. In this second edition (the first appeared in 1998), the authors have changed the organization of the book.

The book is divided into three types of chapters. The first type covers specific dementias such as Alzheimer disease. The second type addresses underlying theories of dementia such as amyloid and amyloid-like protein aggregates. The third type addresses characteristics of dementia, covering topics such as cognitive neuropsychology and advances in neuroimaging. The book is loosely organized so that the etiologic theory chapters precede the chapters on the associated dementias. The chapters addressing clinical features are placed at the rear of the book.

The disease-specific chapters are largely consistent in their approaches and cover diagnostic criteria, clinical features, epidemiology, genetics, and management. These chapters are easy to digest and are filled with valuable information for the clinician. The chapters describing characteristics of the dementias provide practical and current information. The chapters describing the underlying pathologic bases are more variable in their level of complexity. Granted, the complexity of material to be presented is high in these chapters. Moreover, several of the dementias do not fit neatly into a single category. The chapter on amyloid is particularly clear.

Strengths: This is an excellent resource and provides stimulating reading on the clinical consequences of neurodegeneration as well as current diagnostic and management strategies.

Weaknesses: The deficiencies of the text involve inconsistencies in level of detail and complexity of the chapters. Some of the chapters require a sophisticated level of knowledge. The strengths far outweigh the weaknesses.

Recommended Audience: This volume is recommended for clinicians and researchers in the field of dementia who wish to tie together current research with clinical presentation. It is an excellent resource for physicians in training.

Critical Appraisal: This book provides up-to-date information on clinical and research components of dementia. It is interesting and educational to read cover to cover but also is a valuable resource to keep on hand as a reference tool.

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On Being a Doctor 3

Christine Lane, MD, MPH, and Michael A. LaCombe MD, Editors.

Scope: This is the third compilation of short stories and poems submitted to the Editors of Annals of Internal Medicine for their popular “On Being a Doctor,” “On Being a Patient,” and “Ad Libitum” sections that appeared from 1999 to 2006. For more than 15 years, these submissions have filled the odd spaces of the official journal of the American College of Physicians (ACP) with thought-provoking, angering, heart-breaking, and inspiring stories from the “odd spaces” of our lives as physicians and patients.

The book is divided into eight sections that bring the complexities of our “modernized” profession back into
some manageable perspective. With sections dedicated to “On Aging” and “On Death and Dying” being given a prominent place, I was drawn to them first and found works of great heart juxtaposed with stories of grim realities that remind us of our own mortality. These touching stories, along with the realities of the sections on “Hospitals, Health Systems, Contentions” and “On Society and the World Around Us,” provide the volume a balance of values. Other sections emphasize “On Becoming a Doctor,” “Balancing the Personal and Professional,” and “Those Who Are Our Patients.”

The sensitive and the insensitive sides of health care are both presented here. The author compares the long wait for the physician to the shorter wait for the veterinarian.

Strengths: Unless you are a member of the ACP and have kept all the Annals since 1999, you won’t find this heart-filled prose and poetry anywhere but in this well-rounded, night-stand volume. The editors have done an excellent job of picking stories and placing them in an order that reminds us of what we should always strive to be.

Weaknesses: There are none. These stories are each worth reading.

Recommended Audience: This book is for everyone—even nonphysicians. It is the perfect bed-stand digest, especially for those in training. Five minutes with this book every night will keep the heart in the right place.

Critical Appraisal: The editors of Annals of Internal Medicine have given us an excellent collection of prose and poetry that keeps us grounded. It helps to show the world that heartfelt values are still present in medical practice.

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San Francisco, California
Upcoming Meetings

32nd Annual Meeting of the American Society of Neuroimaging
Orlando, FL
Contact: asn@llmsi.com

Chennai Neuro-Ophthalmology Update
Chennai, India
http://www.aios.org/opconference.htm
Contact: drrag@snmail.org

Feb. 18–Feb. 20, 2009
International Stroke Conference
San Diego, CA
http://strokeconference.americanheart.org
Contact: strokeconference@heart.org

Feb. 21–Feb. 26, 2009
Lake Tahoe, CA
http://www.nanosweb.org/meetings/nanos2009/
Contact: info@nanosweb.org

April 17–April 21, 2009
35th American Association of Pediatric Ophthalmology Strabismus (AAPOS) Annual Meeting
San Francisco, CA
http://www.aapos.org
Contact: aapos@aao.org

April 25–May 2, 2009
Annual Meeting of the American Academy of Neurology (AAN)
Seattle, WA
http://www.aan.com/go/am
Contact: memberservices@aan.com

May 3–May 7, 2009
Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting
Ft. Lauderdale, FL
Contact: arvo@arvo.org

May 16–May 19, 2009
Society of Neurological Surgeons Annual Meeting
Salt Lake City, UT
http://www.societyns.org/meeting_info.html
Contact: burchiek@ohsu.edu

May 16–May 21, 2009
47th Annual Meeting of the American Society of Neuroradiology (ASNR)
Vancouver, BC
Contact: meetings@asnr.org

May 26–May 29, 2009
XVIII European Stroke Conference
Stockholm, Sweden
http://www.eurostroke.org/
Contact: hennerici@eurostroke.eu

June 9–June 12, 2009
Canadian Neurological Sciences Federation 44th Annual Congress
Halifax, NS
http://www.cnsfederation.org/general_information_congress.html
Contact: info@cnsfederation.org

June 13–June 16, 2009
17th Congress of the European Society of Ophthalmology
Amsterdam, The Netherlands
http://www.soe2009.org/
Contact: soe2009@congrex.com

June 17–June 20, 2009
9th European Neuro-Ophthalmology Society Meeting
Lubeck, Germany
http://www.eunos2009.org/
Contact: detlef.koempf@neuro.uni-luebeck.de
June 20–June 24, 2009
19th Meeting of the European Neurological Society
Milan, Italy
http://www.akm.ch/ens2009/
Contact: info@ensinfo.org

June 20–June 24, 2009
Canadian Ophthalmological Society Annual Meeting
Toronto, ON
http://www.eyesite.ca/english/amindex.htm
Contact: cos@eyesite.ca

Sept. 10–Sept. 13, 2009
14th International Headache Congress/51st Annual Scientific Meeting
Philadelphia, PA
http://www.americanheadachesociety.org/
Contact: abmsmtgs@talley.com

Sept. 12–Sept. 15, 2009
13th Congress of the European Federation of Neurological Societies (EFNS)
Florence, Italy
http://efns2009.efns.org/
Contact: efns09@kenes.com

Sept. 16–Sept. 18, 2009
32nd Annual Meeting of the Japanese Neuroscience Society
Nagoya, Japan
Contact: neuroscience2009@jnss.org

Sept. 25–Sept. 26, 2009
Practical Pearls in Neuro-Ophthalmology
University of Toronto
Toronto, ON
http://events.cmetoronto.ca/website/index/opt0907
Contact: help-OPT0907@cmetoronto.ca

Sept. 30–Oct. 3, 2009
European Association for Vision and Eye Research (EVER) Annual Congress
Portoroz, Slovenia
http://www.ever.be
Contact: ever@ever.be

134th Annual Meeting of the American Neurological Association
Baltimore, MD
http://www.aneuroa.org
Contact: julieratzloff@llmsi.com

Oct. 17–Oct. 21, 2009
39th Annual Meeting of the Society for Neuroscience
Chicago, IL
http://www.sfn.org
Contact: info@sfn.org

Joint Meeting of the 29th Pan-American Congress of Ophthalmology
113th Annual Meeting of the American Academy of Ophthalmology
San Francisco, CA
http://www.paao.org/congress.html
Contact: info@paao.org

59th Annual Meeting of the Congress of Neurological Surgeons
New Orleans, LA
http://www.neurosurgeon.org/meetings
Contact: info@1cns.org

19th World Congress of Neurology
Bangkok, Thailand
http://www.wcn2009bangkok.com/
Contact: wcn2009@congrex.com

March 6–March 10, 2010
Tucson, AZ
http://www.nanosweb.org/meetings/index.htm
Contact: info@nanosweb.org
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